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(21) International Application Number: PCT/GB96/01810 (22) International Filing Date: 30 July 1996 (30.07.96) (30) Priority Data: 9515975.2 4 August 1995 (04.08.95) GB (71) Applicant (for all designated States except US): ZENECA LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): BOYLE, Francis, Thomas [GB/GB]; ZENECA Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). DAVIES, David, Huw [GB/GB]; ZENECA Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). KENNY, Peter, Wedderburn [GB/GB]; ZENECA Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). MATUSIAK, Zbigniew, Stanley [GB/GB]; ZENECA Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). SC-HOLES, Peter, Beverley [GB/GB]; ZENECA Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). WARDLEWORTH, James, Michael [GB/GB];		ZENECA Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). (74) Agent: GILES, Allen, Franck; Zeneca Pharmaceuticals, Intellectual Property Dept., Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). (81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.	
(54) Title: 4-MERCAPTOPYRROLIDINE DERIVATIVES AS FARNESYL TRANSFERASE INHIBITORS			
(57) Abstract			
Pharmaceutical compositions comprising an inhibitor of ras farnesylation of formula (I) wherein, R ¹ is for example H and further values as defined in the specification; R ² is for example H and further values as defined in the specification; R ³ is for example H or a substituent having values as defined in the specification; p is 0-3 in which R ³ values can be the same or different; L is a linking moiety for example -CO-NH ₂ - and further values as defined in the specification; A is selected from phenyl; naphthyl; a 5-10 membered monocyclic or bicyclic heteroaryl ring containing up to 5 heteroatoms where the heteroatoms are independently selected from O, N and S; or a -S-S- dimer thereof when R ² =H; or an enantiomer, diastereoisomer, pharmaceutically acceptable salt, prodrug or solvate thereof together with a pharmaceutically acceptable diluent or carrier. A particular use is cancer therapy.		<p style="text-align: center;"> $\begin{array}{c} \text{R}^2\text{---S} \\ \\ \text{4} \end{array} \quad \begin{array}{c} \text{2} \\ \\ \text{L---A---(R}^3\text{)}_p \end{array} \quad \text{(I)}$ </p>	

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4-MERCAPTOPYRROLIDINE DERIVATIVES AS FARNESYL TRANSFERASE INHIBITORS

This invention relates to compounds that inhibit farnesylation of mutant ras gene products through inhibition of the enzyme farnesyl-protein transferase (FPTase). The invention also relates to methods of manufacturing the compounds, pharmaceutical compositions and methods of treating diseases, especially cancer, which are mediated through farnesylation of ras.

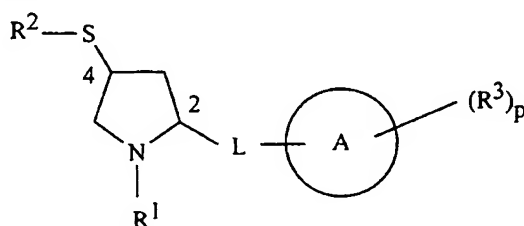
Cancer is believed to involve alteration in expression or function of genes controlling cell growth and differentiation. Whilst not wishing to be bound by theoretical considerations the following text sets out the scientific background to ras in cancer. Ras genes are frequently mutated in tumours: Ras genes encode guanosine triphosphate (GTP) binding proteins which are believed to be involved in signal transduction, proliferation and malignant transformation. H-, K- and N-ras genes have been identified as mutant forms of ras (Barbacid M, Ann. Rev. Biochem. 1987, 56: 779-827). Post translational modification of ras protein is required for biological activity. Farnesylation of ras catalysed by FPTase is believed to be an essential step in ras processing. It occurs by transfer of the farnesyl group of farnesyl pyrophosphate (FPP) to a cysteine at the C-terminal tetrapeptide of ras in a structural motif called the CAAX box. After further post-translational modifications, including proteolytic cleavage at the cysteine residue of the CAAX box and methylation of the cysteine carboxyl, ras is able to attach to the cell membrane for relay of growth signals to the cell interior. In normal cells activated ras is believed to act in conjunction with growth factors to stimulate cell growth. In tumour cells it is believed that mutations in ras cause it to stimulate cell division even in the absence of growth factors (Travis J. Science 1993, 260: 1877-1878), possibly through being permanently in GTP activated form rather than cycled back to GDP inactivated form. Inhibition of farnesylation of mutant ras gene products will stop or reduce activation.

One class of known inhibitors of farnesyl transferase is based on farnesyl pyrophosphate analogues: see for example European patent application EP 534546 from Merck. Inhibitors of farnesyl transferase based on mimicry of the CAAX box have been reported. Reiss (1990) in Cell 62, 81-8 disclosed tetrapeptides such as CVIM (Cys-Val-Ile-Met). James (1993) in Science 260, 1937-1942 disclosed benzodiazepine based

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peptidomimetic compounds. After earliest priority date of the present invention Lerner (1995) in J. Biol. Chem. 270, 26802 and Eisai in International Patent Application WO 95/25086 disclosed further peptidomimetic compounds based on Cys as the first residue. Also after the earliest priority date of the present invention Bristol-Myers Squibb in
 5 European Patent Application EP 696593 disclosed for the first time farnesyl transferase inhibitors having a 4-sulfanylpyrrolidine residue in the first position.

According to one aspect of the present invention there is provided a pharmaceutical composition comprising an inhibitor of ras farnesylation of Formula I



Formula I

10 wherein:

R^1 is selected from H; $-C_{1-4}$ alkyl; $-C_{1-3}$ alkylene-Ph optionally mono or di-substituted on Ph with substituents selected from C_{1-4} alkyl, halogen, OH, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-4} alkanoyloxy, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4} alkanoylamino, nitro, cyano, carboxy, carbamoyl, C_{1-4} alkoxycarbonyl, thiol, C_{1-4} alkylsulfanyl,

15 C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl and sulfonamido; $-CO-C_{1-4}$ alkyl; $-CO-O-C_{1-4}$ alkyl; $-CO-O-C_{2-4}$ alkenyl; $-CO-O-(CH_2)_n$ Ph optionally substituted on Ph as defined for substitution on Ph in $R^1 = -C_{1-3}$ alkylene-Ph above and $n=0-4$;

$-C_{1-4}$ alkylene- $CONR^4R^5$ where R^4 & R^5 are independently selected from H and C_{1-4} alkyl; and $-C_{1-4}$ alkylene- $COOR^6$ where R^6 is selected from H, C_{1-4} alkyl;

20 R^2 is selected from H; $-C_{1-4}$ alkyl; $-C_{1-3}$ alkylene-Ph optionally substituted on Ph as defined for substitution on Ph in $R^1 = -C_{1-3}$ alkylene-Ph above; $-COC_{1-4}$ alkyl; and $-COOC_{1-4}$ alkyl;

R^3 is selected from H; OH; CN; CF_3 ; NO_2 ; $-C_{1-4}$ alkyl; $-C_{1-4}$ alkylene- R^7 where R^7 is selected from phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring

25 containing upto 5 heteroatoms selected from O, N and S and any aryl ring in R^7 is optionally substituted as defined for substitution on the Ph group in $R^1 = -C_{1-3}$ alkylene-Ph above; R^7 ; C_{2-4} alkenyl; halogen; $-(CH_2)_nCOOR^8$ where $n=0-3$ and R^8 represents H,

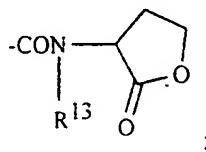
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C₁₋₄alkyl, or C₂₋₄alkenyl; -CONR⁹R¹⁰ where R⁹ and R¹⁰ independently represent H.

C₁₋₄alkyl, C₂₋₄alkenyl, -O-C₁₋₄alkyl, -O-C₂₋₄alkenyl, -C₁₋₃alkylenePh optionally substituted as defined for this group for R¹ above: -CON(R¹¹)OR¹² where R¹¹ and R¹² independently represent H, C₁₋₄alkyl and C₂₋₄alkenyl;

- 5 a group of Formula II, -CONR¹³-CHR¹⁴-COOR¹⁷, where R¹³ is H or C₁₋₄alkyl, R¹⁷ is H or C₁₋₆alkyl, R¹⁴ is selected from the side chain of a lipophilic amino acid, carbamoylC₁₋₄alkyl, N-(monoC₁₋₄alkyl)carbamoylC₁₋₄alkyl and N-(diC₁₋₄alkyl)carbamoylC₁₋₄alkyl, the group of Formula II having L or D configuration at the chiral alpha carbon in the corresponding free amino acid; a lactone of formula



10

C₁₋₄alkyl monosubstituted on carbon with =N-OH;

a group of Formula -X-R¹⁵ where X is selected from O, CO, CH₂, S, SO, SO₂ and R¹⁵ is selected from C₁₋₆alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 5 heteroatoms selected from O, N and S and any aryl ring in

- 15 R¹⁵ is optionally substituted as defined for the Ph group in R¹ = -C₁₋₃alkylene-Ph; p is 0-3 in which R³ values can be the same or different;

L is a linking moiety selected from the following groups written from left to right in Formula I:

-CO-NR¹⁶- where R¹⁶ is selected from H, C₁₋₄alkyl, C₁₋₄alkylene-Z, -CO-

- 20 C₁₋₄alkylene-Z,

-CO-C₁₋₆alkyl, -COZ, Z and Z is selected from -O-C₁₋₄alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 5 heteroatoms selected from O, N and S and any aryl ring in R¹⁶ is optionally substituted as defined for the Ph group in R¹ = -C₁₋₃alkylene-Ph; -CH₂-NR¹⁸- where R¹⁸ represents any value defined for

- 25 R¹⁶; -CH₂S-; -CH₂O-; -CH₂-CHR¹⁹- where R¹⁹ represents any value defined for R¹⁶; -CH=CR²⁰- where R²⁰ represents any value defined for R¹⁶; -CH₂NR²¹-T- where R²¹ represents any value defined for R¹⁶, T represents -(CH₂)_n- where n is 1-4 and T is optionally monosubstituted with R²² where R²² represents any value for R¹⁶ other than H; -CH₂NR²³-SO₂- where R²³ represents any value defined for R¹⁶; -CH₂-NR²⁴-CO-T- where

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R^{24} represents any value defined for R^{16} . T represents $-(CH_2)_n-$ where n is 0-4 and T is optionally monosubstituted with R^{29} where R^{29} represents any value for R^{16} other than H: $-CO-NR^{25}-T-$ where R^{25} represents any value defined for R^{16} . T represents $-(CH_2)_n-$ where n is 1-4 and T is optionally monosubstituted with R^{26} where R^{26} represents any value for R^{16} other than H; $-CH_2S-T-$ where T represents $-(CH_2)_n-$ where n is 1-4 and T is optionally monosubstituted with R^{27} where R^{27} represents any value for R^{16} other than H; $-CH_2O-T-$ where T represents $-(CH_2)_n-$ where n is 1-4 and T is optionally monosubstituted with R^{28} where R^{28} represents any value for R^{16} other than H;

A is selected from phenyl; naphthyl; a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 5 heteroatoms where the heteroatoms are independently selected from O, N & S;

or a -S-S- dimer thereof when $R^2=H$; or a N-oxide thereof;

or an enantiomer, diastereoisomer, pharmaceutically acceptable salt, prodrug or solvate thereof together with a pharmaceutically acceptable diluent or carrier.

15 Preferably R^1 is selected from H; $-CO-O-(CH_2)_nPh$ optionally substituted on Ph as defined for $R^1 = -C_{1-3}alkylene-Ph$ and $n=0-4$; $-CO-O-C_{2-4}alkenyl$; $-CO-C_{1-4}alkyl$; $-C_{1-4}alkylene-CONR^4R^5$ where R^4 & R^5 are independently selected from H, $C_{1-4}alkyl$.

Preferably R^2 is selected from H and $-CO-C_{1-4}alkyl$.

Preferably L is selected from $-CH_2-NR^{18}-$; $-CH_2NR^{21}-T$.

20 Preferably A is selected from phenyl, naphthyl, pyridyl and thienyl.

Preferably combinations of R^3 and p are selected from:

- i) R^3 is selected from a group of Formula II: $-C_{1-4}alkylR^7$; $-O-R^7$ and; R^7 ; and $p=1-3$ with the proviso that one value of R^3 is a group of Formula II;
- ii) $p=0$ with the proviso that A is naphthyl and L is $-CH_2NR^{21}-T$;
- 25 iii) $p=1$ with the proviso that R^3 = a group of Formula II and A is naphthyl.

In another embodiment of the invention it is preferred that:

R^1 is selected from H; $-C_{1-4}alkyl$, $-C_{1-3}alkylene-Ph$ optionally mono or di-substituted on Ph with substituents selected from $C_{1-4}alkyl$, halogen, OH, $C_{1-4}alkoxy$, $C_{1-4}alkanoyl$, $C_{1-4}alkanoyloxy$, amino, $C_{1-4}alkylamino$, $di(C_{1-4}alkyl)amino$, $C_{1-4}alkanoylamino$, thiol, $C_{1-4}alkylthio$, nitro, cyano, carboxy, carbamoyl, $C_{1-4}alkoxycarbonyl$, $C_{1-4}alkylsulfinyl$, $C_{1-4}alkylsulfonyl$, sulfonamido; $-CO-C_{1-4}alkyl$; $-CO-O-C_{1-4}alkyl$;

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- CO-O-C₂₋₄alkenyl; -CO-O-CH₂-Ph optionally mono- or di-substituted on phenyl with substituents selected from C₁₋₄alkyl, halogen, OH, C₁₋₄alkoxy, C₁₋₄alkanoyl, C₁₋₄alkanoyloxy, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, C₁₋₄alkanoylamino, thiol, C₁₋₄alkylthio, nitro, cyano, carboxy, carbamoyl, C₁₋₄alkoxycarbonyl, C₁₋₄alkylthiono.
- 5 C₁₋₄alkylsulfonyl, sulfonamido: -C₁₋₄alkylene-CONR⁴R⁵ where R⁴ & R⁵ are independently selected from H, C₁₋₄alkyl; -C₁₋₄alkylene-COOR⁶ where R⁶ is selected from H, C₁₋₄alkyl;
- R² is selected from H; -C₁₋₄alkyl; -C₁₋₃alkylene-Ph; -COC₁₋₄alkyl; -COOC₁₋₄alkyl; R³ is selected from H; OH; CN; CF₃; NO₂; -C₁₋₄alkyl, -C₁₋₄alkylene-R⁷ where R⁷ is
- 10 selected from phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 3 heteroatoms selected from O, N and S; C₂₋₄alkenyl; halogen: -(CH₂)_nCOOR⁸ where n= 0-3 and R⁸ represents H, C₁₋₄alkyl, C₂₋₄alkenyl; -CONR⁹R¹⁰ where R⁹ and R¹⁰ independently represent H, C₁₋₄alkyl, C₂₋₄alkenyl, -O-C₁₋₄alkyl, -O-C₂₋₄alkenyl;
- 15 -CON(R¹¹)OR¹² where R¹¹ and R¹² independently represent H, C₁₋₄alkyl and C₂₋₄alkenyl; a group of Formula II, -CONR¹³-CHR¹⁴-COOR¹⁷, where R¹³ is H or C₁₋₄alkyl, R¹⁷ is H or C₁₋₆alkyl, R¹⁴ is the side chain of a lipophilic amino acid with L or D configuration at the chiral alpha carbon in the corresponding free amino acid; C₁₋₄alkyl monosubstituted on carbon with =N-OH; -SO-C₁₋₄alkyl; -SO₂-C₁₋₄alkyl;
- 20 a group of Formula -X-R¹⁵ where X is selected from CO, CH₂, S, SO, SO₂ and R¹⁵ is selected from C₁₋₆alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 3 heteroatoms selected from O, N and S;
- p is 0-3 in which R³ values can be the same or different;
- L is a linking moiety selected from the following groups written from left to right in
- 25 Formula I:
- CO-NR¹⁶- where R¹⁶ is selected from H, C₁₋₄alkyl, C₁₋₄alkylene-Z and Z is selected from -O-C₁₋₄alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 3 heteroatoms selected from O, N and S; -CH₂-NR¹⁸- where R¹⁸ represents any value defined for R¹⁶; -CH₂S-; -CH₂O-; -CH₂-CHR¹⁹- where R¹⁹ represents
- 30 any value defined for R¹⁶; -CH=CR²⁰- where R²⁰ represents any value defined for R¹⁶; -CH₂NR²¹-T- where R²¹ represents any value defined for R¹⁶, T represents -(CH₂)_n- where

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n is 1-4 and T is optionally monosubstituted with R^{22} where R^{22} represents any value for R^{16} other than H, and provided at least one of R^{21} and R^{22} is H: $-\text{CH}_2\text{NR}^{23}-\text{SO}_2-$ where R^{23} represents any value defined for R^{16} ; $-\text{CH}_2\text{NR}^{24}-\text{CO}-\text{T}-$ where R^{24} represents any value defined for R^{16} . T represents $-(\text{CH}_2)_n-$ where n is 0-4 and T is optionally monosubstituted with R^{29} where R^{29} represents any value for R^{16} other than H, and provided at least one of R^{24} and R^{29} is H; $-\text{CO}-\text{NR}^{25}-\text{T}-$ where R^{25} represents any value defined for R^{16} . T represents $-(\text{CH}_2)_n-$ where n is 1-4 and T is optionally monosubstituted with R^{26} where R^{26} represents any value for R^{16} other than H, and provided at least one of R^{24} and R^{25} is H; $-\text{CH}_2\text{S}-\text{T}-$ where T represents $-(\text{CH}_2)_n-$ where n is 1-4 and T is optionally monosubstituted with R^{27} where R^{27} represents any value for R^{16} other than H; $-\text{CH}_2\text{O}-\text{T}-$ where T represents $-(\text{CH}_2)_n-$ where n is 1-4 and T is optionally monosubstituted with R^{28} where R^{28} represents any value for R^{16} other than H:

A is selected from phenyl; naphthyl; a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 3 or 5 heteroatoms in the case of monocyclic and bicyclic rings respectively where the heteroatoms are independently selected from O, N & S; or a -S-S- dimer thereof when $R^2=\text{H}$.

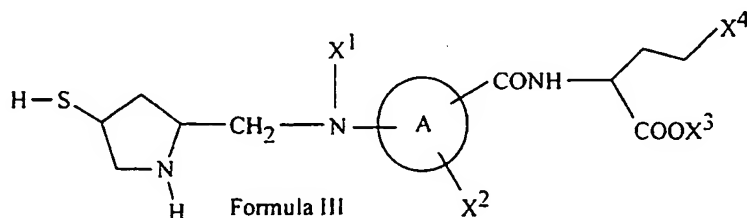
A preferred pharmaceutical composition is in the form of a tablet.

According to another aspect of the invention there is provided a compound of Formula I, III, IV or V for use as a medicament.

20 According to another aspect of the invention there is provided a compound of Formula I, III, IV or V for use in preparation of a medicament for treatment of a disease mediated through farnesylation of ras.

Many compounds of Formula I are a feature of this invention and in particular according to another aspect of the invention there is provided a compound of any of the following classes i), ii) or iii):

class i)



wherein:

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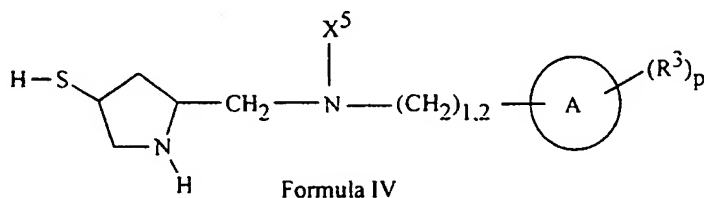
X^1 is selected from H; C_{1-6} alkyl; hydroxy C_{1-6} alkyl; C_{1-6} alkoxy C_{1-6} alkyl; C_{1-6} alkylcarbonyl; hydroxy C_{1-6} alkylcarbonyl; C_{1-6} alkoxy C_{1-6} alkylcarbonyl;

A is selected from phenyl, naphthyl or a 5-10 membered heterocyclic ring having upto 5 heteroatoms selected from O, N and S;

- 5 X^2 is selected from H; phenyl; phenyl C_{1-6} alkyl; a 5-6 membered heteroaryl ring containing upto 3 heteroatoms selected from O, N and S optionally linked to A by C_{1-6} alkyl; and X^2 is optionally substituted on any ring as defined for phenyl in $R^1 = -C_{1-3}$ alkylene-Ph in claim 1;

X^3 is selected from H; C_{1-6} alkyl;

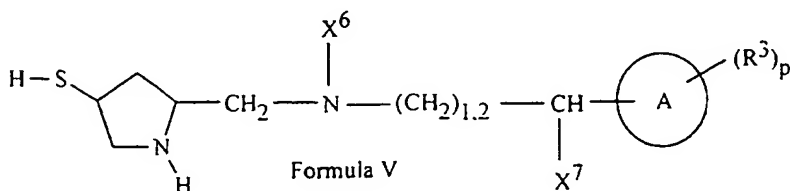
- 10 X^4 is selected from C_{1-6} alkylsulfanyl; C_{1-6} alkylsulfinyl; C_{1-6} alkylsulfonyl; carbamoyl; \underline{N} -(C_{1-6} alkyl)carbamoyl; \underline{N} -(di C_{1-6} alkyl)carbamoyl; and hydroxy or a C_{1-4} alkyl ether thereof: class ii)



wherein:

- 15 X^5 is selected from $-CO-C_{1-4}$ alkyl-Ph; $-CO-C_{1-6}$ alkyl; $-CO-C_{1-4}$ alkyl-heteroaryl where heteroaryl is a 5-10 membered heteroaryl ring containing upto 5 heteroatoms selected from O, N and S and Ph or heteroaryl are optionally substituted as defined for Ph in $R^1 = -C_{1-3}$ alkylene-Ph; C_{1-4} alkyloxy C_{1-4} alkyl;
- 20 A is naphthyl or a 10 membered heterocyclic ring having upto 5 heteroatoms selected from O, N and S;
- R^3 and p are as defined in claim 1;

class iii)



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wherein:

X^6 has any value defined for X^5 in ii) above;

X^7 is Ph optionally substituted as defined for Ph in $R^1 = -C_{1-3}\text{alkylene-Ph}$:

A is Ph or naphthyl or a 5-10 membered heterocyclic ring having upto 5 heteroatoms

5 selected from O, N and S;

R^3 and p are as defined above:

or a N-oxide, pharmaceutically acceptable salt, prodrug or solvate thereof.

Preferred values for compounds of class i) include,

X^1 is selected from H and $C_{1-6}\text{alkoxy}C_{1-6}\text{alkyl}$;

10 X^2 is selected from H; phenyl or phenyl $C_{1-6}\text{alkyl}$;

X^4 is $C_{1-6}\text{alkylsulfanyl}$;

A is selected from phenyl or naphthyl;

Other preferred values for X^4 are -OMe and the lactone which can be formed when X^4 is OH and X^3 is H.

15 Preferred values for compounds of class ii) include p is 0.

Preferred values for compounds of class iii) include,

X^7 is Ph;

A is Ph;

p is 0.

20 In another embodiment of the invention there is provided a compound of Formula I

in which: R^1 is selected from H or $C_{1-4}\text{alkyl}$; R^2 is selected from H, $C_{1-4}\text{alkyl}$,

$-\text{COC}_{1-4}\text{alkyl}$; $-\text{C}_{1-4}\text{alkylPh}$; L is selected from the following values as defined herein.

CONR^{16} , CH_2S , CH_2O , $\text{CH}_2\text{CHR}^{19}$, $\text{CH}=\text{CHR}^{20}$, $\text{CH}_2\text{NR}^{24}\text{COT}$, CONR^{25}T , CH_2ST and

CH_2OT ; and values for A, R^3 and p are as defined herein. with the proviso that 2-

25 (benzylcarbamoyl)-4-sulfanylpyrrolidine and 4-(acetylsulfonyl)-2(benzylcarbamoyl)-

pyrrolidine are excluded. It is believed that the excluded compounds were disclosed as

intermediates for beta-lactam antibiotic synthesis in Japanese patent application 60233076

(Sumitomo Chemical).

According to another aspect of the present invention there is provided any one of

30 the following individual compounds or a pharmaceutically acceptable salt thereof:

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- (2S)-2-{2-Benzyl-5-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-benzoylamino}-4-methylsulfanylbutyric acid methyl ester ;
- (2S)-2-{2-Benzyl-5-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-benzoylamino}-4-methylsulfanylbutyric acid ;
- 5 (2S)-2-({2-phenyl-5-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-phenylcarbonyl)-amino)-4-methylsulfanylbutyric acid methyl ester;
- (2S)-2-({2-phenyl-5-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-phenylcarbonyl)-amino)-4-methylsulfanylbutyric acid;
- (2S)-2-({3-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-naphthalene-1-carbonyl)-amino)-4-methylsulfanylbutyric acid methyl ester ;
- 10 (2S)-2-({3-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-naphthalene-1-carbonyl)-amino)-4-methylsulfanylbutyric acid ;
- (2S)-2-({3-phenyl-5[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-phenylcarbonyl)-amino)-4-methylsulfanylbutyric acid methyl ester;
- 15 (2S)-2-({3-phenyl-5[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-phenylcarbonyl)-amino)-4-methylsulfanylbutyric acid;
- (2S,4S)-2-[{N-(4-methoxybenzyl)-N-(naphthalen-1-ylmethyl)-amino}-methyl]-pyrrolidine-4-thiol ;
- N-(naphthalen-1-ylmethyl)-N-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-pentanamide ;
- 20 N-(naphthalen-1-ylmethyl)-N-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-2-(pyridin-3-yl)-acetamide ;
- N-[(2S,4S)-4-sulfanyl-pyrrolidin-2-ylmethyl]-3-methyl-N-(2-naphthalen-1-yl-ethyl)butyramide ;
- N-[(2S,4S)-4-sulfanyl-pyrrolidin-2-ylmethyl)-N-(2-naphthalen-1-yl-ethyl)-2-pyridin-3-yl-
- 25 acetamide ;
- (2S,4S)-2-{{(3-Methoxypropyl)-(2-naphthalen-1-ylethyl)amino}methyl}-pyrrolidine-4-thiol;
- N-[(2S,4S)-4-sulfanyl-pyrrolidin-2-ylmethyl)-2-(4-methoxy-phenyl)-N-(2-naphthalen-2-yl-ethyl)-acetamide ;
- 30 (2S,4S)-2-{{(2-(4-Methoxyphenyl)ethyl)-(2-naphthalen-1-ylethyl)amino} methyl}-pyrrolidine-4-thiol ;

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N-(2,2-Diphenyl-ethyl)-N-([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-3-methyl-butylamide ;

N-([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-3,3-dimethyl-N-(2-naphthalen-2-yl-ethyl)-butylamide ;

5 N-(2,2-Diphenyl-ethyl)-N-([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-3,3-dimethyl-butylamide ;

(2S)-2-{3-[(2S,4S]-4-Sulfanyl-pyrrolidin-2-ylmethyl)-(3-methoxy-propyl)-amino}-benzoylamino}-4-methylsulfanyl-butyl acid ;

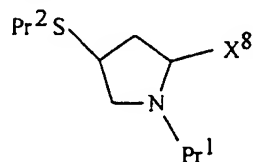
N-([2S,4S]-4-Sulfanyl-pyrrolidin-2-ylmethyl)-3,3-dimethyl-N-(2-naphthalen-1-yl-ethyl)-10 butylamide ;

(2S)-4-Carbamoyl-2-({2-phenyl-5-[(2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-amino}-phenylcarbonyl)-amino)-butyl acid; and

(2S)-4-Carbamoyl-2-({2-phenyl-5-[(2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-amino}-phenylcarbonyl)-amino)-butyl acid methyl ester.

15 According to another aspect of the invention there is provided a pharmaceutical composition comprising a compound as defined in any one Formulas III, IV or V or an individual compound listed above together with a pharmaceutically acceptable diluent or carrier.

According to another aspect of the invention there is provided a process for
20 preparing compounds of classes i), ii) or iii) as defined above which comprises deprotecting a compound of Formula VI



Formula VI

wherein X⁸ represents the right hand side of compound classes i), ii) or iii) as defined above, Pr¹ is H or an amino protecting group, Pr² is H or a thio protecting group and any
25 functional groups in X⁸ are optionally protected with the proviso that there is at least one protecting group and optionally, if desired, converting the product thus obtained into a pharmaceutically acceptable salt thereof.

In an embodiment of the invention:

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Examples of values for R^1 include methyl; $-\text{CH}_2\text{-Ph}$; $-\text{CH}_2\text{-Ph}$ substituted on Ph with nitro, especially 4-nitro; acetyl; BOC; allyloxycarbonyl; $-\text{CO-O-CH}_2\text{-Ph}$ substituted on Ph with nitro, especially 4-nitro; $-\text{CH}_2\text{CONH}_2$.

Examples of values for R^2 include $-\text{COMe}$ and $-\text{COO}^{\text{tert}}\text{butyl}$.

5 Examples of values for R^3 include Cl; $-\text{COOH}$; $-\text{CONH}_2$; $-\text{SOMe}$ and; $-\text{SO}_2\text{Me}$.

When R^3 represents $-(\text{CH}_2)_n\text{-COOR}^8$ a suitable value for n is 0.

Examples of lipophilic amino acids which contribute their side chain (denoted R^{14} within the definition of values for R^3) include methionine, phenylglycine, phenylalanine, serine, leucine, isoleucine or valine. L configuration in the corresponding free amino acid
10 is preferred. Examples of amino acid side chains are set out below. A preferred value for R^{14} is $-\text{CH}_2\text{-CH}_2\text{-S-CH}_3$. Further preferred values for R^{14} are $-\text{CH}_2\text{-OMe}$ and $-\text{CH}_2\text{-CH}_2\text{-OMe}$.

When R^{17} is H to give a COOH group in Formula II, and R^{14} is $-\text{CH}_2\text{-CH}_2\text{-OH}$ then a lactone can be formed where R^{17} and R^{14} together form part of a dihydrofuran-2-one
15 heterocyclic ring. The same lactone can be formed for compounds of Formula III where X^4 is OH and X^3 is H.

Amino Acid	Side Chain
methionine	$-\text{CH}_2\text{-CH}_2\text{-S-CH}_3$
phenylglycine	Ph
phenylalanine	$-\text{CH}_2\text{-Ph}$
serine	$-\text{CH}_2\text{OH}$ or a C_{1-4} alkyl (preferably methyl) ether thereof.
leucine	$-\text{CH}_2\text{-CHMe}_2$
homoserine	$-\text{CH}_2\text{-CH}_2\text{-OH}$ or a C_{1-4} alkyl (preferably methyl) ether thereof.

20 A preferred value for p is 2.

When L is $-\text{CH}_2\text{NR}^{21}\text{-T}$ a suitable value for n is 1. When L is $-\text{CH}_2\text{NR}^{24}\text{-CO-T}$ a suitable value for n is 1. When L is $-\text{CH}_2\text{NR}^{25}\text{-T}$ a suitable value for n is 1. When L is $-\text{CH}_2\text{S-T}$ a suitable value for n is 1. When L is $-\text{CH}_2\text{O-T}$ a suitable value for n is 1. L is especially $-\text{CONH-}$, $-\text{CH}_2\text{-NH-}$, $-\text{CH}_2\text{NHSO}_2\text{-}$, $-\text{CH}_2\text{NHCO-}$.

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Examples of values for A when A is heteroaryl are thienyl, pyridyl, quinolyl & quinoxaliny.

Further preferred values are set out below.

For R¹: 4-nitro-benzyloxycarbonyl; allyloxycarbonyl; carbamoylmethyl; acetyl;

5 phenoxy carbonyl; H.

For R²: Acetylsulfanyl; H.

For R³: Methoxycarbonyl; N-methyl-N-methoxy-carbamoyl; nitro; allyloxycarbonyl; N-methyl-allyloxycarbamoyl; ethoxycarbonyl; 3,4-dichloro-benzyl-carbamoyl; hydroxy; carboxy; (2S),4-methylsulfanyl-butyric acid methyl ester-2yl-carbamoyl;

10 (2S),4-methylsulfanyl-butyric acid-2yl-carbamoyl; phenoxy.

For p: 1-2, especially 2; a further preferred value is 0.

For L: -C(O)-NH-; -CH₂-C(O)-NH-; -CH₂-NH-C(O)-; -CH₂-NH-SO₂-; especially -C(O)-NH-.

For A: phenyl; pyridyl, thienyl; naphthyl.

15 For R¹⁶ & R¹⁸⁻²⁶: H, C₁₋₄alkyl, especially H.

In another embodiment of the invention preferred values are set out below.

In compounds of Formula III: X¹ is H or methoxyC₁₋₄alkyl (especially H); X² is H, phenyl or benzyl (especially benzyl); X³ is H or C₁₋₄alkyl (especially H); X⁴ is

C₁₋₄alkylsulfanyl (especially methylsulfanyl); and A is phenyl. When A is a 6-membered

20 aryl or heteroaryl ring then groups -NX¹- and the substituent comprising X⁴ are preferably in meta juxtaposition relative to each other; and X², if present, is preferably positioned para relative to -NX¹-. The chiral carbon to which -COOX³ is attached is preferably in S configuration. The chiral carbons at the 2 and 4 positions of the pyrrolidine ring are preferably in S configuration.

25 In compounds of Formula IV: X⁵ is -CO-C₁₋₄alkyl (especially -CO-CH₂-CHMe₂) or -CH₂-Ph-O-C₁₋₄alkyl (especially -CH₂-Ph-OMe); heteroaryl is preferably pyridyl and a preferred aryl or heteroaryl substituent is -O-C₁₋₄alkyl (especially methoxy); and A is naphthyl. The chiral carbons at the 2 and 4 positions of the pyrrolidine ring are preferably in S configuration. The attachment point for A relative to -(CH₂)_{1,2}- is preferably at the 1
30 position of naphthalene and the equivalent position for heterocyclic values for A

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(regardless of ring numbering conventions for heterocycles). A preferred value for $-(CH_2)_{1,2}-$ is $-(CH_2)_2-$.

In compounds of Formula V: X^b is $-CO-C_{1-3}alkyl$ (more preferably $-CO-CH_2-CHMe_2$ or $-CO-CH_2-t-butyl$, especially $-CO-CH_2-CHMe_2$) or $-CH_2-Ph-O-C_{1-4}alkyl$ (especially $-CH_2-Ph-OMe$); heteroaryl is preferably pyridyl and a preferred aryl substitution is $-O-C_{1-4}alkyl$ (especially methoxy); and A is phenyl or naphthyl (especially phenyl). The chiral carbons at the 2 and 4 positions of the pyrrolidine ring are preferably in S configuration. A preferred value for $-(CH_2)_{1,2}-$ is $-(CH_2)_1-$.

Suitable pairs of values for R^3 when $p=2$ are: $-COOMe$, $-CO.N(Me).OMe$; NO_2 , $-CO.N(Me).OMe$; $-COOMe$, allyloxycarbonyl; $-CO.N(Me).OMe$, allyloxycarbonyl; allyloxycarbonyl, $-CO.N(Me).O.CH_2CH=CH_2$; OH , $COOH$; $-COOMe$, $COOMe$; Ph , $-CO.N-Methionine$ methyl ester; Ph , $-CO.N-Methionine$; benzyl, $-CO.N-Methionine$ methyl ester; benzyl, $-CO.N-Methionine$; benzyl, $-CO.N-Methionine$ isopropyl ester; Ph , $-CO.N\alpha-Glutamine$ methyl ester; Ph , $-CO.N\alpha-Glutamine$.

Suitable values for $L = CHNR^{21}T$ include $CH_2.N(CO.CH_2.CHMe_2).CH_2.CH_2$; $CH_2.N(CH_2.CH_2.CH_2OMe).CH_2.CH_2$; $CH_2.N(CH_2.pPh.OMe).CH_2.CH_2$; $CH_2.N(CO.CH_2.CHMe_2).CH_2$; $CH_2.N(CO.CH_2.CH_2.CH_2.Me).CH_2$; $CH_2.N(CO.CH_2.CHMe.CH_2Me).CH_2$; $CH_2.N(CO.CH_2.CH_2.OMe).CH_2$; $CH_2.N(CO.CH_2.pyridin-3-yl).CH_2$; $CH_2.N(4-methoxybenzyl).CH_2$; $CH_2.N(CO.CH_2.CHMe_2).CH_2.CH_2.CH(Ph)$; $CH_2.N(CO.CH_3).CH_2.CH_2.CH(Ph)$; $CH_2.N(CO.CH_2.CHMe_2).CH_2$; $CH_2.N(CO.CH_3).CH_2$; $CH_2.N(CO.CH_2.CHMe_2).CH_2.CH(Ph)$; $CH_2.N(CO.CH_2.CMe_3).CH_2.CH(Ph)$; $CH_2.N(CO.CH_2.pyridin-3-yl).CH_2.CH(Ph)$; $CH_2.N(CO.1-hydroxy-6-methoxy-pyridin-3-yl).CH_2.CH(Ph)$; $CH_2.N(CO.CH_2.CHMe_2).CH_2.CH_2$; $CH_2.N(CO.CH_2.CMe_3).CH_2.CH_2$; $CH_2.N(CO.CH_2.pyridin-3-yl).CH_2.CH_2$; $CH_2.N(CO.4-methoxybenzyl).CH_2.CH_2$;

Suitable values for $L = -CH_2NR^{18}-$ include CH_2NH ; CH_2NMe ; $CH_2.N(CO.CH_2.CHMe_2)$ and $CH_2.N(CO.CH_2.CH_2.OMe)$.

Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

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- a) Design of Prodrugs, edited by H. Bundgaard. (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396. edited by K. Widder. *et al.* (Academic Press, 1985);
- b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard. Chapter 5 "Design and Application of Prodrugs". by H. Bundgaard
- 5 p. 113-191 (1991);
- c) H. Bundgaard. Advanced Drug Delivery Reviews. 8, 1-38 (1992);
- d) H. Bundgaard. *et al.*. Journal of Pharmaceutical Sciences. 77, 285 (1988); and
- e) N. Kakeya, *et al.*. Chem Pharm Bull. 32, 692 (1984).

Examples of pro-drugs include *in vivo* hydrolysable esters of a compound of the

10 Formula I. An *in vivo* hydrolysable ester of a compound of the formula (I) containing carboxy group is, for example, a pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to produce the parent acid. Suitable pharmaceutically-acceptable esters for carboxy include C₁₋₆alkoxymethyl esters for example methoxymethyl, C₁₋₆alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters. C₃₋

15 ₈cycloalkoxycarbonyloxyC₁₋₆alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C₁₋₆alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

Particular substitutions on A for 6 membered rings are in the meta or para

20 positions.

Some compounds within the scope of Formula I are known as intermediates in carbapenem side chain synthesis but it is believed that they have not been previously described in forms suitable as pharmaceutical compositions nor had any pharmaceutical activity associated with them *per se*. The reader is referred to the following publications in

25 this regard and also in respect of synthetic details for compound preparation: Matsumura, Heterocycles (1995), 41, 147-59; European patent application EP 590885 (Zeneca; Betts *et al.*); European patent application EP 592167 (Zeneca; Siret); European patent application EP 562855 (Zeneca; Jung *et al.*); International patent application WO 92/17480 (Imperial Chemical Industries; Betts *et al.*); European patent application EP 508682 (Imperial

30 Chemical Industries; Betts *et al.*); European Patent Application EP 280771 (Fujisawa Pharmaceutical. Murata *et al.*); and International patent application WO 92/17479 (Imperial

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Chemical Industries; Betts *et al*).

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as "propyl" are specific for the straight-chain version only and references to individual
5 branched-chain alkyl groups such as "isopropyl" are specific for the branched-chain version only. An analogous convention applies to other generic terms.

It is to be understood that, insofar as certain of the compounds of Formula I defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active
10 or racemic form which possesses the property of inhibiting FTPase. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, inhibitory properties against FTPase may be evaluated using the standard laboratory techniques referred to hereinafter.

15 The term " halogen " refers to fluorine, chlorine, bromine and iodine. The term " carbamoyl " refers to $-C(O)NH_2$. The term " BOC " refers to *tert*-butyl-O-C(O)-. The term " allyl " refers to $CH_2=CH-CH_2-$. Bicyclic aryl and bicyclic heteroaryl rings refer to ring systems in which both rings of the bicyclic system are aromatic.

Examples of C_{1-6} alkyl include methyl, ethyl, propyl, isopropyl, *sec*-butyl, *tert*-butyl
20 and pentyl; examples of C_{1-4} alkyl include methyl, ethyl, propyl, isopropyl, *sec*-butyl and *tert*-butyl; examples of C_{1-3} alkyl include methyl, ethyl, propyl and isopropyl; examples of $-C_{1-3}$ alkylenePh include benzyl, phenylethyl, phenylpropyl; examples of C_{1-4} alkoxy (also called $-O-C_{1-4}$ alkyl herein) include methoxy, ethoxy and propoxy; examples of C_{1-4} alkanoyl include formyl, acetyl and propionyl; examples of C_{1-4} alkanoyloxy
25 include acetyloxy and propionyloxy; examples of C_{1-4} alkylamino include methylamino, ethylamino, propylamino, isopropylamino, *sec*-butylamino and *tert*-butylamino; examples of $di-(C_{1-4}alkyl)amino$ include di-methylamino, di-ethylamino and *N*-ethyl-*N*-methylamino; examples of $C_{1-4}alkanoylamino$ include acetamido and propionylamino; examples of $C_{1-4}alkoxycarbonyl$ include methoxycarbonyl, ethoxycarbonyl and
30 propoxycarbonyl; examples of $C_{1-4}alkylsulfanyl$ include methylsulfanyl, ethylsulfanyl, propylsulfanyl, isopropylsulfanyl, *sec*-butylsulfanyl and *tert*-butylsulfanyl; examples of

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- C₁₋₄alkylsulfinyl** include methylsulfinyl, ethylsulfinyl, propylsulfinyl, isopropylsulfinyl, *sec*-butylsulfinyl and *tert*-butylsulfinyl; examples of **C₁₋₄alkylsulfonyl** include methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, *sec*-butylsulfonyl and *tert*-butylsulfonyl; examples of **-CO-C₁₋₄alkyl** include formyl, acetyl, propionyl, butyryl, and valeryl; examples of **-CO-O-C₁₋₄alkyl** include ethyloxycarbonyl, propyloxycarbonyl and *tert*-butyloxycarbonyl (BOC);
- examples of **-CO-O-C₂₋₄alkenyl** include allyloxycarbonyl and vinyloxycarbonyl;
- examples of **-CO-O-(CH₂)_nPh** where n=0-4 include phenyloxycarbonyl, benzyloxycarbonyl, phenylethyloxycarbonyl and phenylpropyloxycarbonyl;
- examples of **-C₁₋₄alkylene-CONR⁴R⁵** include carbamoylmethyl, carbamoylethyl, N-methylcarbamoylethyl, N-methyl-N-ethylcarbamoylethyl; examples of **-C₁₋₄alkylene-COOR⁶** include carboxymethyl, carboxyethyl, carboxypropyl, propionic acid methyl ester, acetic acid ethyl ester; examples of **C₂₋₄alkenyl** include allyl and vinyl; examples of **-O-C₂₋₄alkenyl** include allyloxy and vinyloxy; examples of **lipophilic amino acids** include valine, leucine, isoleucine, methionine, phenylalanine, serine, threonine and tyrosine; examples of **carbamoylC₁₋₄alkyl** include carbamoylmethyl, carbamoylethyl and carbamoylpropyl; examples of **N-(monoC₁₋₄alkyl)carbamoylC₁₋₄alkyl** include N-methylcarbamoylmethyl and N-ethylcarbamoylethyl; examples of **N-(diC₁₋₄alkyl)carbamoylC₁₋₄alkyl** include N,N-dimethylcarbamoylethyl and N-methyl-N-ethylcarbamoylethyl;
- examples of **C₁₋₄alkyl monosubstituted on carbon with =N-OH** include butyraldehyde oxime and propionaldehyde oxime; examples of **hydroxyC₁₋₆alkyl** include hydroxymethyl, hydroxyethyl, hydroxypropyl, 2-hydroxypropyl, 2-(hydroxymethyl)propyl and hydroxypentyl; examples of **C₁₋₆alkoxyC₁₋₆alkyl** include methoxyethyl, ethoxyethyl and methoxybutyl; examples of **C₁₋₆alkylcarbonyl** include methylcarbonyl, ethylcarbonyl, propylcarbonyl, isopropylcarbonyl, *sec*-butylcarbonyl, *tert*-butylcarbonyl and pentylcarbonyl; examples of **hydroxyC₁₋₆alkylcarbonyl** include hydroxyacetyl, hydroxypropionyl, hydroxybutyryl, 3-hydroxybutyryl and hydroxypentanoyl; examples of **C₁₋₆alkoxyC₁₋₆alkylcarbonyl** include methoxyacetyl, methoxypropionyl, ethoxybutyryl and butoxyacetyl; examples of **phenylC₁₋₆alkyl** include benzyl, phenylethyl and phenylpropyl; examples of **-CO-C₁₋₄alkyl-Ph** include phenylacetyl and phenylpropionyl; examples of **-CO-C₁₋₄alkyl-heteroaryl** include 2-(3-pyridyl)-acetyl and 2-(3-thienyl)-

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acetyl: examples of N-(C₁₋₆alkyl)carbamoyl include N-methyl-carbamoyl and N-ethyl-carbamoyl: examples of N-(diC₁₋₆alkyl)carbamoyl include N,N-dimethylcarbamoyl and N-methyl-N-ethylcarbamoyl.

Examples of 5-10 membered monocyclic or bicyclic heteroaryl rings containing
5 upto 5 heteroatoms selected from O,N and S include the following.

Examples of 5- or 6-membered heteroaryl ring systems include imidazole, triazole, pyrazine, pyrimidine, pyridazine, pyridine, isoxazole, oxazole, isothiazole, thiazole and thiophene. A 9 or 10 membered bicyclic heteroaryl ring system is an aromatic bicyclic ring system comprising a 6-membered ring fused to either a 5 membered ring or another 6
10 membered ring. Examples of 5/6 and 6/6 bicyclic ring systems include benzofuran, benzimidazole, benzthiophene, benzthiazole, benzisothiazole, benzoxazole, benzisoxazole, pyridoimidazole, pyrimidoimidazole, quinoline, isoquinoline, quinoxaline, quinazoline, phthalazine, cinnoline and naphthyridine.

Preferably monocyclic heteroaryl rings contain upto 3 heteroatoms and bicyclic
15 heteroaryl rings contain upto 5 heteroatoms. Preferred heteroatoms are N and S, especially N. In general, attachment of heterocyclic rings to other groups is via carbon atoms. Suitable values of heterocycles containing only N as the heteroatom are pyrrole, pyridine, indole, quinoline, isoquinoline, imidazole, pyrazine, pyrimidine, purine and pteridine.

Preferably any chiral carbon atoms at the 2 and 4 positions of the pyrrolidine
20 ring in Formulas I and III-V are in S configuration.

Compounds of Formula I and III-V may form salts which are within the ambit of the invention. Pharmaceutically acceptable salts are preferred although other salts may be useful in, for example, isolating or purifying compounds.

When the compound contains a basic moiety it may form pharmaceutically
25 acceptable salts with a variety of inorganic or organic acids, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. A suitable pharmaceutically-acceptable salt of the invention when the compound contains an acidic moiety is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an
30 organic base which affords a pharmaceutically-acceptable cation, for example a salt with

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methyllamine. dimethylamine. trimethylamine. piperidine. morpholine or tris-(2-hydroxyethyl)amine.

Solvates, for example hydrates, are also within the ambit of the invention and may be prepared by generally known methods.

5 According to another aspect of the present invention there is provided a compound of Formula I for use as a medicament.

According to another aspect of the present invention there is provided the use of a compound of Formula I in preparation of a medicament for treating ras mediated diseases, especially cancer.

10 According to another aspect of the present invention there is provided a method of treating ras mediated diseases, especially cancer, by administering an effective amount of a compound of Formula I to a mammal in need of such treatment.

According to a further feature of the invention there is provided a compound of Formula I, or a pharmaceutically-acceptable salt thereof, for use in a method of
15 treatment of the human or animal body by therapy.

The invention also includes a method of treating a disease or medical condition mediated alone or in part by farnesylated ras which comprises administering to a mammal requiring such treatment an effective amount of an active ingredient as defined above. The invention also provides the use of such an active ingredient in the production
20 of a new medicament for use in a farnesylated ras mediated disease or medical condition.

Specific cancers of interest include:

- carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, ovary, pancreas, stomach, cervix, thyroid and skin;
- hematopoietic tumors of lymphoid lineage, including acute lymphocytic
25 leukemia, B-cell lymphoma and Burketts lymphoma;
- hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias and promyelocytic leukemia;
- tumors of mesenchymal origin, including fibrosarcoma and
rhabdomyosarcoma; and
- 30 - other tumors, including melanoma, seminoma, tetratocarcinoma, neuroblastoma and glioma.

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The compounds of Formula I are especially useful in treatment of tumors having a high incidence of ras mutation, such as colon, lung, and pancreatic tumors. By the administration of a composition having one (or a combination) of the compounds of this invention, development of tumors in a mammalian host is reduced.

5 Compounds of Formula I may also be useful in the treatment of diseases other than cancer that may be associated with signal transduction pathways operating through Ras, e.g., neuro-fibromatosis.

 Compounds of Formula I may also be useful in the treatment of diseases associated with CAAX-containing proteins other than Ras (e.g., nuclear lamins and
10 transducin) that are also post-translationally modified by the enzyme farnesyl protein transferase.

 The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams,
15 ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

20 The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

 Suitable pharmaceutically acceptable excipients for a tablet formulation include,
25 for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to
30 modify their disintegration and the subsequent absorption of the active ingredient within

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the gastrointestinal tract. or to improve their stability and/or appearance. in either case. using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent. for example. calcium carbonate.
5 calcium phosphate or kaolin. or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil. liquid paraffin. or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents. such as sodium carboxymethylcellulose. methylcellulose. hydroxypropylmethylcellulose. sodium alginate.
10 polyvinyl-pyrrolidone. gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxyethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols. for example heptadecaethyleneoxycetanol. or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as
15 polyoxyethylene sorbitol monooleate. or condensation products of ethylene oxide with long chain aliphatic alcohols. for example heptadecaethyleneoxycetanol. or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate. or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides. for example polyethylene
20 sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate. anti-oxidants (such as ascorbic acid). colouring agents. flavouring agents. and/or sweetening agents (such as sucrose. saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a
25 vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax. hard paraffin or cetyl alcohol. Sweetening agents such as those set out above. and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

30 Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a

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dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

5 The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an
10 esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol,
15 propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents,
20 which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Suppository formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the
25 rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating an active ingredient with a conventional, topically acceptable, vehicle or diluent using conventional procedure
30 well known in the art.

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Compositions for administration by insufflation may be in the form of a finely divided powder containing particles of average diameter of, for example, 30 μ or much less. the powder itself comprising either active ingredient alone or diluted with one or more physiologically acceptable carriers such as lactose. The powder for insufflation is then
5 conveniently retained in a capsule containing, for example, 1 to 50mg of active ingredient for use with a turbo-inhaler device, such as is used for insufflation of the known agent sodium cromoglycate.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an
10 aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on Formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of
15 Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active
20 agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch;
25 Chairman of Editorial Board), Pergamon Press 1990.

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine. As mentioned above, compounds of the Formula I are
30 useful in treating diseases or medical conditions which are due alone or in part to the effects of farnesylation of ras.

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In using a compound of the Formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.5 mg to 75 mg per kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for
5 intravenous administration, a dose in the range, for example, 0.5 mg to 30 mg per kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.5 mg to 25 mg per kg body weight will be used. Oral administration is however preferred.

Compounds of this invention may be useful in combination with known
10 anti-cancer and cytotoxic agents. If formulated as a fixed dose such combination products employ the compounds of this invention within the dosage range described herein and the other pharmaceutically active agent within its approved dosage range. Sequential use is contemplated when a combination formulation is inappropriate.

Although the compounds of the Formula I are primarily of value as therapeutic
15 agents for use in warm-blooded animals (including man), they are also useful whenever it is required to inhibit the effects of activation of ras by farnesylation. Thus, they are useful as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents.

According to another aspect of the present invention there is provided
20 individual compounds produced as end products in the Examples set out below and salts thereof.

A compound of the invention, or a salt thereof, may be prepared by any process known to be applicable to the preparation of such compounds or structurally related compounds. Such processes are illustrated by the following representative schemes
25 in which variable groups have any of the meanings defined for Formula I unless stated otherwise. Functional groups may be protected and deprotected using conventional methods. For examples of protecting groups such as amino and carboxylic acid protecting groups (as well as means of formation and eventual deprotection), see T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis", Second Edition, John
30 Wiley & Sons, New York, 1991. Note abbreviations used have been listed immediately before the Examples below.

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Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

5 Specific examples of protecting groups are given below for the sake of convenience, in which "lower" signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not
10 specifically mentioned is of course within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or araliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms).

Examples of carboxy protecting groups include straight or branched chain
15 (1-12C)alkyl groups (e.g. isopropyl, *t*-butyl); lower alkoxy lower alkyl groups (e.g. methoxymethyl, ethoxymethyl, isobutoxymethyl; lower aliphatic acyloxy lower alkyl groups, (e.g. acetoxymethyl, propionyloxymethyl, butyryloxymethyl, pivaloyloxymethyl); lower alkoxycarbonyloxy lower alkyl groups (e.g. 1-methoxycarbonyloxyethyl, 1-ethoxycarbonyloxyethyl); aryl lower alkyl groups (e.g. *p*-methoxybenzyl, *o*-nitrobenzyl,
20 *p*-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (e.g. trimethylsilyl and *t*-butyldimethylsilyl); tri(lower alkyl)silyl lower alkyl groups (e.g. trimethylsilylethyl); and (2-6C)alkenyl groups (e.g. allyl and vinyllethyl).

Methods particularly appropriate for the removal of carboxyl protecting groups include for example acid-, metal- or enzymically-catalysed hydrolysis.

25 Examples of hydroxy protecting groups include lower alkenyl groups (e.g. allyl); lower alkanoyl groups (e.g. acetyl); lower alkoxy carbonyl groups (e.g. *t*-butoxycarbonyl); lower alkenyloxycarbonyl groups (e.g. allyloxycarbonyl); aryl lower alkoxy carbonyl groups (e.g. benzoyloxycarbonyl, *p*-methoxybenzyloxycarbonyl, *o*-nitrobenzyloxycarbonyl, *p*-nitrobenzyloxycarbonyl); tri lower alkyl/arylsilyl groups (e.g. trimethylsilyl,
30 *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl); aryl lower alkyl groups (e.g. benzyl) groups; and triaryl lower alkyl groups (e.g. triphenylmethyl).

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Examples of amino protecting groups include formyl, aralkyl groups (e.g. benzyl and substituted benzyl, e.g. p-methoxybenzyl, nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-p-anisylmethyl and furylmethyl groups; lower alkoxy carbonyl (e.g. t-butoxycarbonyl); lower alkenyloxycarbonyl (e.g. allyloxycarbonyl); aryl lower

5 alkoxy carbonyl groups (e.g. benzyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl; trialkylsilyl (e.g. trimethylsilyl and t-butyl dimethylsilyl); alkylidene (e.g. methylenediphenyl); benzylidene and substituted benzylidene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include,

10 for example, acid-, base, metal- or enzymically-catalysed hydrolysis, or photolytically for groups such as o-nitrobenzyloxycarbonyl, or with fluoride ions for silyl groups.

Examples of protecting groups for amide groups include aralkoxymethyl (e.g. benzyloxymethyl and substituted benzyloxymethyl); alkoxymethyl (e.g. methoxymethyl and trimethylsilylethoxymethyl); tri alkyl/arylsilyl (e.g. trimethylsilyl, t-butyl dimethylsilyl, t-

15 butyldiphenylsilyl); tri alkyl/arylsilyloxymethyl (e.g. t-butyl dimethylsilyloxymethyl, t-butyl diphenylsilyloxymethyl); 4-alkoxyphenyl (e.g. 4-methoxyphenyl); 2,4-di(alkoxy)phenyl (e.g. 2,4-dimethoxyphenyl); 4-alkoxybenzyl (e.g. 4-methoxybenzyl); 2,4-di(alkoxy)benzyl (e.g. 2,4-di(methoxy)benzyl); and alk-1-enyl (e.g. allyl, but-1-enyl and substituted vinyl e.g. 2-phenylvinyl).

20 Aralkoxymethyl, groups may be introduced onto the amide group by reacting the latter group with the appropriate aralkoxymethyl chloride, and removed by catalytic hydrogenation. Alkoxymethyl, tri alkyl/arylsilyl and tri alkyl/silyloxymethyl groups may be introduced by reacting the amide with the appropriate chloride and removing with acid; or in the case of the silyl containing groups, fluoride ions. The alkoxyphenyl and alkoxybenzyl

25 groups are conveniently introduced by arylation or alkylation with an appropriate halide and removed by oxidation with ceric ammonium nitrate. Finally alk-1-enyl groups may be introduced by reacting the amide with the appropriate aldehyde and removed with acid.

Compounds of Formula I in which L represents $-CO-NR^{16}-$ may be prepared by forming an amide bond between compounds 1 and 2 as outlined in Scheme 23.

30 Compounds of Formula I in which L represents $-CO-NR^{25}-T-$ may be prepared by an analogous procedure. Suitable coupling conditions include the following.

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- i) Use of EEDQ at room temperature in an organic solvent (e.g. dichloromethane, methanol).
- ii) Use of oxalyl chloride in an organic solvent (e.g. DMF, CH_2Cl_2) in the presence of an organic base (e.g. NMM, triethylamine, DMAP) at 0° to room temperature
5 for 0.5-16h.
- iii) Use of EDC/ HOBT in an organic solvent (e.g. DMF, CH_2Cl_2).
- iv) Use of DCCI/ HOBT in an organic solvent (e.g. DMF, CH_2Cl_2) in the presence of an organic base (e.g. triethylamine).
- v) Use of mixed anhydride reactions under standard conditions, for example
10 isopropylchloroformate in an organic solvent (e.g. DMF, DMA, dichloromethane) in the presence of an organic base (e.g. NMM, DMAP, triethylamine).
- vi) Via an active ester under standard conditions e.g. pentafluorophenyl ester in an organic solvent (e.g. dichloromethane) in the presence of an organic base (e.g. triethylamine).
- 15 vii) Via an acid chloride under standard conditions e.g. using thionyl chloride and heat for about 150min followed by an organic base (e.g. triethylamine) in the presence of an organic solvent (e.g. acetonitrile).

Compounds of Formula I in which L represents $-\text{CH}_2\text{NR}^{18}-$, $-\text{CH}_2\text{O}-$ or $-\text{CH}_2\text{S}-$ may be prepared as outlined in Scheme 24. LG represents a leaving group (e.g. mesyloxy, tosyloxy, halogen) and X represents S, O or NR^{18} . Suitable coupling conditions include the following.

- i) Use of an inorganic base (e.g. NaHCO_3 , NaH, K_2CO_3 , butyllithium) in an organic solvent (e.g. THF, DMF, DMSO) and a temperature of about 70° to 150°
- ii) Use of an organic base (e.g. triethylamine, DMAP) in an organic solvent (e.g. THF, dichloromethane, DMA, DMF) at a temperature range of room temperature -150°
25
- iii) Use of an inorganic base (e.g. KOH, NaOH, K_2CO_3) in an aqueous (e.g. water) and organic solvents (e.g. dichloromethane) in a 2 phase system, optionally in the presence of a phase transfer catalyst (e.g. tetrabutylammoniumbromide).

Compounds of Formula I in which L represents $-\text{CH}=\text{CR}^{20}-$ may be prepared
30 using a Wittig reaction as outlined in Scheme 25. Suitable reaction conditions include the following.

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i) Use of a base (e.g. potassium carbonate, metal hydride, metal alkoxide) in the presence of an organic solvent (e.g. THF, toluene, DMSO) optionally in the presence of an aqueous solvent (2-phase system) and optionally in the presence of a catalyst complexing agent which solubilises alkali metal ions in non-polar solvents such as

- 5 1.4.7.10.13-pentaoxacyclopentadecane (also called 15-Crown-5) or
1.4.7.10.13.16-hexaoxacyclooctadecane (also called 18-Crown-6).

Compounds of Formula I in which L represents $-\text{CH}_2\text{-NR}^{18}-$ may be prepared as outlined in Scheme 26 by coupling aldehyde (2) with compound 4. Suitable coupling conditions include the following.

- 10 i) Use of a reducing agent (e.g. NaCNBH_3 , BH_3 , hydrogen plus catalyst, LiHBEt_3 , di-isobutyl-aluminiumhydride, lithium aluminium hydride, sodium borohydride) in the presence of a suitable solvent e.g. ethanol & acetic acid.

Aldehyde (2) may be prepared by oxidation of the corresponding alcohol (1) under suitable conditions such as use of an oxidising agent (e.g. TPAP, NMM-O) in the
15 presence of an organic solvent (e.g. acetonitrile, dichloromethane) at room temperature. Other suitable oxidising agents include chromium oxide, pyridinium chlorochromate, pyridinium dichromate, sodium dichromate and sodium hypochlorite.

Aldehyde (2) may also be prepared by reduction of the corresponding ester (1) under standard conditions using for example diisobutyl-aluminium hydride.

- 20 Compounds of Formula I in which L represents $-\text{CH}_2\text{-NR}^{21}\text{-T-}$, $-\text{CH}_2\text{-O-T-}$ or $-\text{CH}_2\text{-S-T-}$ may be prepared as outlined in Scheme 27 in which LG represents a leaving group (e.g. mesyloxy, tosyloxy, halogen) and X represents O, S or NR^{21} . Suitable coupling conditions are as outlined above in relation to Scheme 24. Optionally the positions of LG and XH in compounds 1 & 2 in Scheme 27 can be reversed to give the same end product.

- 25 Compounds of Formula I in which L represents $-\text{CH}_2\text{-NR}^{23}\text{-SO}_2\text{-}$ may be prepared as outlined in Scheme 28. Compounds 1 & 2 may be coupled under standard conditions such as the following.

- i) Use of an organic base (e.g. di-isopropyl-ethylamine, triethylamine, 4-methyl-morpholine) in the presence of an organic solvent (e.g. dichloromethane) at a
30 temperature range of $0^\circ - 40^\circ$

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ii) Use of an inorganic base (e.g. potassium carbonate) in the presence of an organic solvent (e.g. DMF) at a temperature range of 0°-150°

Compounds of Formula I in which L represents $-\text{CH}_2\text{-NR}^{24}\text{-CO-T-}$ may be prepared as outlined in Scheme 29. Compounds 1 & 2 may be coupled under standard conditions such as described above for L = $-\text{CO-NR}^{16}\text{-}$.

Compounds of Formula I in which L represents $-\text{CH}_2\text{-CHR}^{19}\text{-}$ may be prepared as by reduction of compounds of the type set out as compound 3 in Scheme 25 but substituting R^{19} in lieu of R^{20} . Reduction is carried out under standard conditions with standard reagents for example using hydrogenation in the presence of a catalyst such as palladium on charcoal at room temperature.

Biological activity was tested as follows. Farnesyl protein transferase (FPT) was partially purified from human placenta by ammonium sulphate fractionation followed by a single Q-Sepharose[®] (Pharmacia, Inc) anion exchange chromatography essentially as described by Ray and Lopez-Belmonte (Ray K P and Lopez-Belmonte J (1992) Biochemical Society Transactions 20 494-497). The substrate for FPT was Kras (CVIM C-terminal sequence). The cDNA for oncogenic val12 variant of human c-Ki-ras-2 4B was obtained from the plasmid pSW11-1 (ATCC). This was then subcloned into the polylinker of a suitable expression vector e.g. pIC147. The Kras was obtained after expression in the E. coli strain, BL21. The expression and purification of c-KI-ras-2 4B and the val12 variant in E. coli has also been reported by Lowe et al (Lowe P N et al. J. Biol. Chem. (1991) 266 1672-1678).

Incubations with enzyme contained 300nM tritiated farnesyl pyrophosphate (DuPont/New England Nuclear), 120nM ras-CVIM, 50mM Tris HCl pH 8.0, 5mM MgCl_2 , 10 μM ZnCl_2 , 5mM dithiothreitol and compounds were added at appropriate concentrations in DMSO (3% final concentration in test and vehicle control). Incubations were for 20 minutes at 37 ° and were stopped with acid ethanol as described by Pompliano et al. (Pompliano D L et al (1992) 31 3800-3807). Precipitated protein was then collected onto glass fibre filter mats (B) using a Tomtec[®] cell harvester and tritiated label was measured in a Wallac[®] 1204 Betaplate scintillation counter.

Although the pharmacological properties of the compounds of the Formula I vary with structural change as expected, in general compounds of the Formula I possess an

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IC₅₀ in the above test in the range. for example. 0.01 to 200µM. Thus by way of example, the compound

5 {[(2S,4S)-4-acetylsulfanyl-1-(4-nitro-benzyloxycarbonyl)-pyrrolidine-2-carbonyl]-amino}-3(N-methyl-methoxycarbamoyl)-benzoic acid allyl ester (see Example 7) has an IC₅₀ of approximately 0.5µM. No physiologically unacceptable toxicity was observed at the effective dose for compounds tested of the present invention.

The invention will now be illustrated in the following non-limiting Examples in which, unless otherwise stated:-

- 10 (i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids by filtration;
- (ii) operations were carried out at room temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon;
- (iii) column chromatography (by the flash procedure) and medium pressure
15 liquid chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385) or Merck Lichroprep RP-18 (Art. 9303) reversed-phase silica obtained from E. Merck, Darmstadt, Germany;
- (iv) yields are given for illustration only and are not necessarily the maximum attainable;
- 20 (v) the end-products of the Formula I have satisfactory microanalyses and their structures were confirmed by nuclear magnetic resonance (NMR) and mass spectral techniques: chemical shift values were measured on the delta scale; the following abbreviations have been used: s, singlet; d, doublet; t or tr, triplet; m, multiplet; br, broad;
- (vi) intermediates were not generally fully characterised and purity was assessed by
25 thin layer chromatographic, infra-red (IR) or NMR analysis;
- (vii) melting points are uncorrected and were determined using a Mettler SP62 automatic melting point apparatus or an oil-bath apparatus; melting points for the end-products of the Formula I were determined after crystallisation from a conventional organic solvent such as ethanol, methanol, acetone, ether or hexane, alone or in admixture:
- 30 and

- 30 -

(viii) the following abbreviations have been used:-

	BOC	<u>tert</u> -butoxycarbonyl
	DCCI	1,3-dicyclohexylcarbodiimide
	DMA	<u>N,N</u> -dimethylacetamide
5	DMAP	4-dimethyl-aminopyridine
	DMF	<u>N,N</u> -dimethylformamide
	DMSO	dimethylsulfoxide
	EDC	1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide
	EEDQ	2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline
10	HOBT	1-hydroxybenzotriazole
	NMM	<u>N</u> -methymorpholine
	NMM-O	4-methymorpholine- <u>N</u> -oxide
	TFA	trifluoroacetic acid
	THF	tetrahydrofuran
15	TMSI	trimethylsilyliodide
	TPAP	tetrapropylammonium perruthenate

Note in the Schemes only those hydrogen atoms thought to assist clarity have been illustrated (ie not all hydrogen atoms have been illustrated).

20

Example 1 (see Scheme 1)

(2S,4S)-4-acetylsulfanyl-2[3-nitro-5-(N-methoxy-N-methyl-carbamoyl)-phenylcarbamoyl]-pyrrolidine-1-carboxylic acid 4-nitro-benzyl ester

25

A mixture of 4-acetylsulfanyl-pyrrolidine-1,2-dicarboxylic acid 1-(4-nitrobenzyl) ester (1(c)) (0.2 g) and 3-amino-N-methoxy-N-methyl-5-nitro-benzamide (1(b)) (0.122 g) and EEDQ (0.201 g) in dichloromethane (20 ml) was stirred at ambient temperature for 16 hours. The solution was then stirred with 0.3M hydrochloric acid (20 ml) for ten minutes. The organic phase was separated, dried over magnesium sulphate and

30

evaporated under reduced pressure to give a gum. This was purified by chromatography

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using 1.ethyl acetate/hexane (50:50) 2.ethyl acetate/hexane (75:25) to give the desired product (1) as a colourless gum (0.132 g).

NMR Spectrum (CDCl₃) δ 2.35 (s, 3H), 2.62 (m, 2H), 3.4 (s, 3H), 3.44 (m, 1H), 3.6 (s, 3H), 4.1 (m, 2H), 4.59 (t, 1H), 5.3 (m, 2H), 7.55 (d, 2H), 8.09 (m, 1H), 8.25 (d, 2H), 8.3 (m, 1H), 8.6 (m, 1H), 9.55 (br. s, 1H).

Starting material (1(c)) was synthesised as described in Reference Example 1-4 in European patent no 126587 (Sumitomo).

Starting material (1(b)) was prepared as follows. A mixture of 3-amino-5-nitrobenzoic acid (10 g), pentafluoro-phenol (10 g) and DCCI (11.3 g) was stirred at ambient temperature for 24 hours. The reaction mixture was filtered and the filtrate poured onto a chromatography column which was then eluted with ethyl acetate/hexane (10:90) to give 3-amino-5-nitrobenzoic acid 2,3,4,5,6-pentafluorophenyl ester (1(a)) as a yellow solid (5.8 g).

NMR Spectrum (CDCl₃) δ 4.3 (br. s, 2H), 7.7 (tr, 1H), 7.8 (tr, 1H), 8.36 (tr, 1H).

A mixture of (1(a)) (1.0 g), N,O-dimethylhydroxylamine HCl salt (0.84 g) and triethylamine (1.82 ml) in dichloromethane (50 ml) was stirred at ambient temperature for 48 hours. Water (50 ml) was added and the mixture stirred for a further 5 minutes. The organic phase was separated, dried over magnesium sulphate and evaporated under reduced pressure to give a gum. This was purified by chromatography using 1. ethyl acetate/hexane (10:90), 2. ethyl acetate/hexane (50:50) as eluents to give starting material 3-amino-N-methoxy-N-methyl-5-nitro benzamide (1(b)) as a yellow solid (0.55 g).
NMR Spectrum: (CDCl₃) δ 3.36 (s, 3H), 3.58 (s, 3H), 7.26 (tr, 1H), 7.56 (tr, 1H), 7.90 (tr, 1H).

25 Example 2 (see Scheme 2)

(2S,4S)-4-acetylsulfanyl-2[3-(N-methoxy-N-methylcarbamoyl)-5-nitro-phenylcarbamoyl]-pyrrolidine-1-carboxylic acid allyl ester

A mixture of (2S,4S)-4-acetylsulfanyl-pyrrolidine-1,2-dicarboxylic acid 1-allyl ester (1(d)) (0.2 g), 1(b) (0.165 g), and EEDQ (0.271 g), in dichloromethane (20 ml) was stirred at ambient temperature for 16 hours. The solution was then stirred with 0.3M

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hydrochloric acid for a further 10 minutes. The organic phase was then separated, dried over magnesium sulphate and evaporated under reduced pressure. The product obtained was purified by column chromatography using ethyl acetate/hexane (50:50) as eluent to give the desired product (2) as a colourless gum (0.152 g).

5 NMR Spectrum (CDCl₃) δ 2.33 (s, 3H), 2.62 (m, 2H), 3.38 (m, 1H), 3.4 (s, 3H), 3.6 (s, 3H), 4.05 (m, 2H), 4.59 (tr, 1H), 4.69 (d, 2H), 5.3 (m, 2H), 5.95 (m, 1H), 8.14 (t, 1H), 8.28 (tr, 1H), 8.6 (tr, 1H), 9.7 (br.s, 1H).

Synthesis of starting material (1(d)) is described as "Compound (A)" on page 10 31 of International Patent Application No. WO 92/17479 (Imperial Chemical Industries). Synthesis of starting material (1(b)) is described in Example 1.

Example 3 (see Scheme 3)

5-[[[(2S,4S),4-acetylsulfanyl-1-(4-nitrobenzyloxycarbonyl)-pyrrolidine-2-carbonyl]-
15 **amino}-isophthalic acid 1-allyl ester 3-methyl ester**

DMF (0.07 ml) was added to a stirred solution of oxalyl chloride (0.078 ml) in dichloromethane (20 ml) cooled to -20° under an argon atmosphere. After 15 minutes a solution of (1(c)) (0.3 g; see Example 1) in dichloromethane was added followed by a
20 solution of N-methylmorpholine (0.099 ml) in dichloromethane (2 ml). After a further 15 minutes a solution of 5-amino-isophthalic acid allyl ester methyl ester (3(b)) (0.192g) in dichloromethane (5 ml) was added again followed by a solution of N-methylmorpholine (0.099 ml) in dichloromethane (2 ml). The mixture was allowed to warm to ambient temperature and stirred for 16 hours. The reaction mixture was poured onto a flash column
25 and eluted with 1. ethyl acetate/hexane (50:50) and, 2. ethyl acetate/hexane (75:25) to give the desired end product (3) as a colourless gum (0.24 g).

NMR Spectrum (CDCl₃) δ 2.33 (s, 3H), 2.62 (m, 2H), 3.45 (m, 1H), 3.95 (s, 3H), 4.03 (m, 1H), 4.17 (m, 1H), 4.57 (tr, 1H), 4.85 (m, 2H), 5.32 (m, 2H), 5.36 (m, 2H), 6.05 (m, 1H), 7.51 (m, 2H), 8.20 (m, 2H), 8.32
30 (m, 2H), 8.34 (s, 1H), 9.2 (br. s, 1H).

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Starting material (3(b)) was synthesised as follows. A mixture of mono-methyl-5-nitroisophthalate (13.8 g), allyl bromide (7.96 g), potassium carbonate (13.94 g) and DMF (160ml) was stirred at ambient temperature for 4.5 h. The solid was filtered and DMF was evaporated away from the filtrate under reduced pressure. The residue was dissolved in diethyl ether (300 ml) and water (100 ml) and stirred for five minutes. The organic layer was separated and washed with saturated sodium bicarbonate solution (220 ml), brine (200ml), dried over magnesium sulphate and evaporated under reduced pressure to give 5-nitro-isophthalic acid allyl ester methyl ester (3(a)) as a yellow oil (14.74 g).

10 NMR spectrum (CDCl₃) δ 4.0 (s, 3H), 4.9 (m, 2H), 5.4 (m, 2H), 6.1 (m, 1H), 9.0 (m, 3H).

A mixture of (3(a)) (15.46 g), tin (II) chloride dihydrate (65.78 g) and methanol (200 ml) was stirred at reflux for 4 hours. Methanol was evaporated under reduced pressure and the residue redissolved in ethyl acetate (400 ml). Ammonia solution (sp. g. 0.880) was added dropwise until the mixture reached pH 8 and no more precipitate was being formed. The solid was then filtered and the filtrate was washed with water (100 ml), brine (100 ml), dried over magnesium sulphate and evaporated under reduced pressure to give starting material 3(b) as a yellow solid (13.56 g).

NMR spectrum (CDCl₃) δ 3.91 (s, 3H), 3.94 (s, 2H), 4.82 (m, 2H), 5.35 (m, 2H), 6.05 (m, 1H), 7.52 (m, 2H), 8.08 (m, 1H).

20

Example 4 (see Scheme 4)

5-([(2S,4S),4-acetylsulfanyl-1-(carbamoylmethyl)-pyrrolidine-2-carbonyl]-amino}-isophthalic acid 1-allyl ester 3-methyl ester

25

A mixture of

5-([(2S,4S),4-acetylsulfanyl-pyrrolidine-2-carbonyl]-amino}-isophthalic acid 1-allyl ester 3-methyl ester TFA salt (4(e)) (0.12 g), iodoacetamide (0.085 g), sodium bicarbonate (0.058 g) and DMF (3.0 ml) was stirred at ambient temperature for 16 h. The DMF was evaporated under reduced pressure and the residue purified by

30 chromatography using 1. ethyl acetate/hexane (60:40), 2. ethyl acetate and, 3.

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methanol/ethyl acetate (5:95) as eluents to give the desired product 4 as a yellow solid (0.055 g).

NMR spectrum δ 2.19 (2 tr. 1H), 2.29 (s, 3H), 2.82 (m, 1H), 3.22 (m, 2H), 3.48 (q, 2H), 3.6 (m, 1H), 3.94 (s, 3H), 4.05 (m, 1H), 4.85 (m, 2H), 5.35 (m, 2H), 6.04 (m, 1H), 6.1 (br. s, 1H), 6.30 (br. s, 1H), 8.43 (m, 1H), 8.55 (m, 1H), 10.46 (br. s, 1H).

Starting material 4(e) was prepared as follows. A mixture of (2S,4S),4-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (1.0 g), EEDQ (1.6 g), Compound (3(b)) (see Example 3) and dichloromethane (100 ml) was stirred at ambient temperature for 16 hours.

The mixture was poured onto a flash column and eluted with 1. ethyl acetate/hexane (80:20) and 2. ethyl acetate to give

5-{[(2S,4S),4-hydroxy-1-(tert-butoxycarbonyl)-pyrrolidine-2-carbonyl]-amino}-isophthalic acid 1-allyl ester 3-methyl ester

(4(a)) as a colourless gum (0.85 g.).

NMR Spectrum (DMSO-d₆) δ 1.34 (2s, 9H), 1.97 (m, 1H), 2.15 (m, 1H), 3.30 (m, 1H), 3.46 (m, 1H), 3.9 (s, 3H), 4.32 (m, 2H), 4.84 (d, 2H), 5.06 (d, 1H), 5.35 (m, 2H), 6.07 (m, 1H), 8.18 (m, 1H), 8.54 (m, 2H).

A mixture of (4(a)) (0.8 g), methanesulphonyl chloride (0.152 ml), triethylamine (0.256 ml), and dichloromethane (20 ml) was stirred at 5° under an argon atmosphere for 10 minutes and then at ambient temperature for 2h. Water (20 ml) was then added and the mixture stirred for another 5 minutes. The organic phase was separated, dried over magnesium sulphate and evaporated under reduced pressure. The product was purified by chromatography using 1. ethyl acetate/hexane (30:70) and 2. ethyl acetate/hexane (80:20) as eluents to give

5-{[(2S,4S),4-methanesulfanyloxy-1-(tert-butoxycarbonyl)-pyrrolidine-2-carbonyl]-amino}-isophthalic acid 1-allyl ester 3-methyl ester (4(b)) as a clear oil (0.8 g).

NMR spectrum (CDCl₃) δ 1.5 (s, 9H), 2.4 (m, 1H), 2.92 (m, 1H), 3.07 (s, 3H), 3.63 (m, 1H), 3.9 (m, 1H), 3.95 (s, 3H), 4.66 (m, 1H), 4.85 (m, 2H), 5.27 (m, 1H), 5.36 (m, 2H), 6.05 (m, 1H), 8.37 (m, 3H), 9.64 (br. s, 1H).

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A mixture of 4(b) (0.74 g), potassium thioacetate (0.32 g) and acetone (25 ml) was maintained at reflux for 18 hours. The mixture was then cooled to room temperature and acetone evaporated under reduced pressure. The residue was dissolved in a mixture of ethyl acetate (50 ml), 1.5M hydrochloric acid (25 ml), and ice (25 ml). The organic phase
5 was separated, dried over magnesium sulphate and evaporated under reduced pressure to give a red gum. This was purified by chromatography using 1. ethyl acetate/hexane (30:70) and, 2. ethyl acetate/hexane(70:30) to give
5-{[(2S,4S),4-acetylsulfanyl-1-(~~tert~~-butoxycarbonyl)-pyrrolidine-2-carbonyl]-amino}-isophthalic acid 1-allyl ester 3-methyl ester
10 (4(c)) as an orange gum (0.48 g).

NMR spectrum (CDCl₃) δ 1.5 (s, 9H), 2.32 (s, 3H), 2.56 (m, 2H), 3.33 (m, 1H), 3.93 (s, 3H), 4.04 (m, 2H), 4.52 (tr, 1H), 4.85 (m, 2H), 5.35 (m, 2H), 6.05 (m, 1H), 8.38 (m, 3H), 9.63 (br. s, 1H).

A mixture of (4(c)) (3.6 g) and TFA (80 ml) was stirred at ambient
15 temperature for 10 minutes. TFA was evaporated under reduced pressure and the residue dissolved in ethyl acetate (200 ml.) and saturated sodium bicarbonate solution (100 ml). This was then stirred for 10 minutes, the organic phase separated, washed with water (100 ml) and brine (100 ml) and dried over magnesium sulphate. The ethyl acetate was removed under reduced pressure and the residue purified by chromatography using 1. ethyl
20 acetate/hexane (30:70), 2. ethyl acetate/hexane (80:20) as eluents to give 4(f) (the free base which is used in Example 6) as a brown oil (2.3 g). NMR Spectrum (CDCl₃) δ 2.05 (m, 1H), 2.30 (s, 3H), 2.42 (br. s, 1H), 2.78 (m, 2H), 3.58 (m, 1H), 3.85 (m, 1H), 3.94 (s, 3H), 3.99 (m, 1H), 4.84 (m, 2H), 5.35 (m, 2H), 6.05 (m, 1H), 8.47 (m, 3H), 9.83 (br. s, 1H).

A mixture of (4(c)) (0.45 g) and TFA (10 ml) was stirred at ambient
25 temperature for 10 minutes. The TFA was evaporated away under reduced pressure and the residue purified by column chromatography using 1 ethyl acetate/hexane (30:70), 2 ethyl acetate/hexane (60:40), 3 ethyl acetate and, 4 methanol/ethyl acetate (10:90) as eluents to give the desired starting material (4(e)) as a brown gum (0.46 g).
NMR Spectrum (CDCl₃) δ 2.15 (m, 1H), 2.33 (s, 3H), 2.97 (m, 1H), 3.44
30 (m, 1H), 3.91 (s, 3H), 3.97 (m, 1H), 4.08 (m, 1H), 4.82 (d, 2H), 4.98 (tr, 1H), 5.35 (m, 2H), 6.03 (m, 1H), 8.12 (m, 2H), 8.26 (m, 1H).

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Example 5 (see Scheme 5)**5-{{(2S,4S),4-acetylsulfanyl-1-acetyl-pyrrolidine-2-carbonyl}-amino}-isophthalic acid 1-allyl ester 3-methyl ester**

A mixture of (4(e)) (0.08 g; see Example 4), triethylamine (0.083 ml), acetic anhydride (0.056 ml) and dichloromethane (5 ml) was maintained at reflux for 16 hours. The mixture was cooled, evaporated under reduced pressure and purified by chromatography using 1 ethyl acetate/hexane (70:30), 2 ethyl acetate and, 3 methanol/dichloromethane (5:95) to give the desired product 5 as a colourless gum (0.048 g).

NMR Spectrum (CDCl₃) δ 2.18 (s, 3H), 2.35 (s, 3H), 2.48 (m, 1H), 2.77 (m, 1H), 3.42 (m, 1H), 3.95 (s, 3H), 4.1 (m, 2H), 4.85 (m, 3H), 5.35 (m, 2H), 6.06 (m, 1H), 8.40 (m, 3H), 9.88 (br. s, 1H).

Starting material 4(e) was prepared as described in Example 4.

Example 6 (see Scheme 6)**5-{{(2S,4S),4-acetylsulfanyl-1-phenyloxycarbonyl-pyrrolidine-2-carbonyl}-amino}-isophthalic acid 1-allyl ester 3-methyl ester**

A mixture of (4(f)) (0.07g), phenyl chloroformate (0.026 ml), triethylamine (0.07 ml) and dichloromethane (3 ml) was stirred at ambient temperature for 16 hours. The mixture was then evaporated under reduced pressure to give a gum which was purified by chromatography using 1 dichloromethane, 2 ethyl acetate/hexane (30:70) and, 3 ethyl acetate/hexane (60:40) to give the desired product as a colourless gum (0.048 g).

NMR Spectrum (DMSO-d₆) δ 1.93-2.24 (m, 1H), 2.38 (s, H), 2.70 (m, 1H), 3.63 (m, 1H), 3.91 (d, 3H), 4.18 (m, 2H), 4.60 (m, 1H), 4.87 (tr, 2H), 5.38 (m, 1H), 6.08 (m, 1H), 6.70-7.69 (m, 5H), 8.20-8.53 (m, 3H), 10.61 (d, 1H).

Starting material 4(f) was prepared as described in Example 4.

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Example 7 (see Scheme 7)

5{[(2S,4S),4-acetylsulfanyl-1-(4-nitro-benzyloxycarbonyl)-pyrrolidine-2-carbonyl]-amino}-3(N-methyl-methoxycarbamoyl)-benzoic acid allyl ester

5 A mixture of (1(c)) (0.02 g; see Example 1), 3-amino- 5(N-methyl-methoxycarbamoyl)-benzoic acid allyl ester (7(d)) (0.16 g.), EEDQ (0.25 g) and dichloromethane (20 ml) was stirred for 16 h at ambient temperature. The mixture was then washed with 0.3M hydrochloric acid (30 ml), the organic phase separated, dried over magnesium sulphate and evaporated to dryness under reduced pressure. The residue was
 10 purified by column chromatography using ethyl acetate/hexane (75:25) as eluent to give the desired product 7 as a yellow solid (0.053 g).

NMR Spectrum (CDCl₃) δ 2.33 (s, 3H), 2.60 (m, 2H), 3.38 (s, 3H), 3.42 (m, 1H), 3.60 (s, 3H), 4.04 (m, 1H), 4.15 (m, 1H), 4.55 (m, 1H), 4.83 (m, 2H), 5.30 (m, 2H), 5.35 (m, 2H), 6.04 (m, 1H), 7.52 (m, 2H), 8.10
 15 (m, 3H), 8.18 (m, 2H), 9.12 (br. s, 1H).

Starting material (1(c)) was prepared as described in Example 1. Starting material 7(d) was prepared as follows. A mixture of potassium carbonate (17.00 g), 5-nitroisophthalic acid (52.00 g), allyl bromide and dimethylacetamide (400 ml) was stirred at 90° for 4 h. Dimethylacetamide was evaporated away under reduced pressure
 20 and the residue was dissolved in ethyl acetate, washed with water (2 x 300 ml) and then extracted with aqueous saturated sodium bicarbonate solution (3 x 300 ml). The extracts were combined, acidified to pH 4 with concentrated hydrochloric acid and reextracted with ethyl acetate (2 x 300 ml). The extracts were combined, washed with water (300 ml), dried over magnesium sulphate and evaporated under reduced pressure to give
 25 5-nitro-isophthalic acid 3-allyl ester (7(a)) as a cream solid (39.48 g).

NMR Spectrum (CDCl₃/DMSOd₆) δ 4.90 (m, 2H), 5.42 (m, 2H), 6.08 (m, 1H), 9.00 (m, 3H).

A solution of 7(a) (10.00 g), N-hydroxysuccinimide (5.04 g) and DCCI (9.03 g) in dichloromethane (400 ml) was stirred at ambient temperature for 3.5 h. The white
 30 precipitate which formed was filtered off and the filtrate evaporated under reduced pressure

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to give a yellow oil. This was purified by flash chromatography eluting with ethyl acetate/hexane (75:25) to give

5-nitro-isophthalic acid 1-(2,5-dioxo-pyrrolidin-1-yl) ester 3-allyl ester (7(b)) as a yellow solid (7.58 g).

5 NMR Spectrum (CDCl₃) δ 2.95 (s, 4H), 4.92 (m, 2H), 5.43 (m, 2H), 6.07 (m, 1H), 9.12 (m, 3H).

A mixture of (7(b)) (2.00 g), N,Q-dimethylhydroxylamine hydrochloride (0.62 g), triethylamine (0.86 ml) and dichloromethane (60 ml) was stirred at 5° for 30 min and then allowed to warm to ambient temperature and stirred for a further 16 h. The mixture
10 was poured onto a flash column and eluted with ethyl acetate/hexane (40:60) to give 3-(N-methyl-methoxycarbamoyl)-5-nitro benzoic acid allyl ester (7(c)) as a yellow oil. NMR Spectrum (CDCl₃) δ 3.43 (s, 3H), 3.58 (s, 3H), 4.90 (m, 2H), 5.40 (m, 2H), 6.07 (m, 1H), 8.71 (m, 1H), 8.76 (m, 1H), 8.95 (m, 1H).

A mixture of (7(c)) (1.11 g), tin(II) chloride dihydrate (4.26 g) and methanol
15 (60 ml) was heated under reflux for 1 hour. The reaction mixture was cooled and the methanol evaporated away under reduced pressure. The residue was redissolved in ethyl acetate (100 ml) and ammonia solution (sp. g. 0.880) was added dropwise until the solution reached pH 8. The precipitate that formed was filtered and washed with ethyl acetate (2 x 100 ml). The combined filtrate and washings were evaporated under reduced pressure to
20 give the desired starting material 3-amino-5-(N-methyl-methoxycarbamoyl)-benzoic acid allyl ester (7(d)) as a white solid (0.610 g).

NMR Spectrum (CDCl₃) δ 3.35 (s, 3H), 3.59 (s, 3H), 3.90 (br. s, 2H), 4.82 (m, 2H), 5.35 (m, 2H), 6.04 (m, 1H), 7.15 (m, 1H), 7.45 (m, 1), 7.72 (m, 1H).

25

Example 8 (see Scheme 8)

5{[(2S,4S),4-acetylsulfanyl-1-(4-nitro-benzyloxycarbonyl)-pyrrolidine-2-carbonyl]-amino}-3(N-methyl-allyloxycarbamoyl)-benzoic acid allyl ester

30 A mixture of (1(c)) (0.293 g; see Example 1), 3-amino- 5(N-methyl-allyloxycarbamoyl)-benzoic acid allyl ester (8(c)) (0.210 g), EEDQ (0.268 g) and

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dichloromethane (20 ml) was stirred at ambient temperature for 16 hours. The mixture was then washed with 0.3M hydrochloric acid (30 ml), dried over magnesium sulphate and placed straight onto a flash column eluting with ethyl acetate/hexane (75:25). The product obtained was placed onto a flash column eluting with methanol/dichloromethane (2.5:97.5) to give the desired product 8 as a clear gum (0.153 g).

NMR Spectrum (CDCl₃) δ 2.33 (s, 3H), 2.61 (m, 2H), 3.40 (s, 3H), 3.42 (m, 1H), 4.04 (m, 1H), 4.15 (m, 1H), 4.26 (d, 2H), 4.55 (m, 1H), 4.83 (m, 2H), 5.30 (m, 6H), 5.75 (m, 1H), 6.04 (m, 1H), 7.53 (m, 2H), 8.12 (m, 2H), 8.21 (m, 3H), 9.12 (br. s, 1H).

10

Starting material (8(c)) was prepared as follows. A mixture of 7(b) (2.00 g; see Example 7), N-methylhydroxylamine hydrochloride (1.06 g) triethylamine (1.72 ml) and dichloromethane (60 ml.) was stirred at 5° for 30 minutes. It was then allowed to warm to ambient temperature and stirred for a further 16 hours. The reaction mixture was then poured directly onto a flash column eluting with ethyl acetate/hexane (50:50) to give 3-(N-methyl-hydroxycarbamoyl)-5-nitro-benzoic acid allyl ester (8(a)) as a cream solid (1.43 g).

NMR Spectrum (CDCl₃) δ 3.48 (s, 3H), 4.90 (m, 2H), 5.42 (m, 2H), 6.05 (m, 1H), 8.28 (br. s, 1H), 8.55 (m, 1H), 8.63 (m, 1H), 8.96 (m, 1H).

20

A mixture of (8(a)) (0.60 g), allyl bromide (0.28 g), potassium carbonate (0.59 g) and DMF (20 ml) was stirred for 3 hours at ambient temperature under an argon atmosphere. The dimethyl formamide was then evaporated under reduced pressure and the residue dissolved in ethyl acetate (50 ml) and water (50ml). The organic phase was separated, washed with brine (50 ml), dried over magnesium sulphate and evaporated under reduced pressure to dryness to give 3-(N-methyl-allyloxycarbamoyl)-5-nitro-benzoic acid allyl ester (8(b)) as a yellow oil (0.571 g).

NMR Spectrum δ 3.47 (s, 3H), 4.25 (m, 2H), 4.90 (m, 2H), 5.35 (m, 4H), 5.65 (m, 1H), 6.06 (m, 1H), 8.73 (m, 1H), 8.78 (m, 1H), 8.95 (m, 1H).

30

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A mixture of (8(b)) (0.523 g), tin(II) chloride dihydrate (1.84 g) and ethyl acetate (50 ml) was heated under reflux for 6 hours. The mixture was allowed to cool to ambient temperature and ammonia solution (sp. g. 0.880) was added dropwise until the solution reached pH 8. The white precipitate which had formed was filtered off, washed with ethyl acetate (2 x 50 ml) and the combined washings and filtrate evaporated to dryness to give the desired starting material (8(c)) as a yellow oil (0.472 g).
NMR Spectrum (CDCl₃) δ 3.38 (s, 3H), 3.88 (m, 2H), 4.25 (d, 2H), 4.80 (m, 2H), 5.32 (m, 4H), 5.75 (m, 1H), 6.03 (m, 1H), 7.15 (m, 1H), 7.45 (m, 1H), 7.75 (m, 1H).

10

Example 9 (see Scheme 9)

5-{[(2S,4S),1-(allyloxycarbonyl)-4-sulfanyl-pyrrolidine-2-carbonyl]-amino}-3(N-methyl-allyloxycarbamoyl)-benzoic acid allyl ester

15 An aqueous solution of 0.1M sodium hydroxide (4.41 ml) was added to a solution of 5-{[(2S,4S),4-acetylsulfanyl-1-(allyloxycarbonyl)-pyrrolidine-2-carbonyl]-amino}-3(N-methyl-allyloxycarbamoyl)-benzoic acid allyl ester (9(a)) in allyl alcohol (15 ml) and the mixture was then stirred at ambient temperature for 1 hour. Hydrochloric acid (1.5M) was then added to bring the solution to pH3 and it was then
20 evaporated to dryness under reduced pressure. The residue was dissolved in ethyl acetate (40 ml) and washed with water (2 x 40 ml). The organic phase was separated, dried over magnesium sulphate and evaporated to dryness to give a yellow foam. This was purified by chromatography using ethyl acetate/hexane (75:25) as eluent to give the desired product 9 as a yellow gum (0.148 g).

25 NMR Spectrum (CDCl₃) δ 1.88 (d, 2H), 2.62 (m, 2H), 3.37 (s, 3H), 3.45 (m, 2H), 3.60 (s, 3H), 4.08 (m, 1H), 4.52 (tr, 1H), 4.65 (m, 2H), 4.83 (m, 2H), 5.35 (m, 4H), 6.00 (m, 2H), 8.10 (m, 1H), 8.15 (m, 1H), 8.21 (m, 1H), 9.15 (br. s, 1H).

30 Starting material 9(a) was prepared as follows. A mixture of 7(d) (0.568 g; see Example 7), 1(d) (0.645 g; see Example 20), EEDQ (0.585 g) and dichloromethane (50

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ml) was stirred at ambient temperature for 16 hours. The mixture was then washed with 0.3M hydrochloric acid(50 ml), dried over magnesium sulphate and applied to a flash column eluting with ethyl acetate/hexane (75:25). It was further purified with a second column eluting with ethyl acetate/hexane (50:50) to give the desired starting material (9(a))

5 as a colourless gum (0.401 g).

NMR Spectrum (CDCl₃) δ 2.33 (s, 3H), 2.60 (m, 2H), 3.37 (s, 3H), 3.40 (m, 1H), 3.61 (s, 3H), 4.02 (m, 1H), 4.13 (m, 1H), 4.58 (tr, 1H), 4.68 (m, 2H), 4.83 (m, 2H), 5.35 (m, 4H), 6.00 (m, 2H), 8.10 (m, 1H), 8.14 (m, 1H), 8.22 (m, 1H), 9.30 (br. s, 1H).

10

Example 10 (see Scheme 10)

5-[((2S,4S),1-allyloxycarbonyl-4-sulfanyl-pyrrolidin-2-yl-methyl)-carbamoyl]-pyridine-2-carboxylic acid methyl ester

15

To a stirring solution of

5-[((2S,4S),1-allyloxycarbonyl-4-BOCsulfanyl-pyrrolidin-2-yl-methyl)-carbamoyl]-pyridine-2-carboxylic acid methyl ester (10(a)) (991 mg; 2.07 mmole) in dichloromethane. TFA (6 mL; 78 mmole) was added dropwise. The solution was stirred, under argon, for 4 hours. The solvent and excess TFA were removed in vacuo. The

20 residue was azeotroped with toluene (2 x 10 mL). Keeping exposure to air to a minimum the resultant oil was triturated with diethyl ether (20 mL). The resultant solid was washed with cold diethyl ether (10 mL) and dried under high vacuum yielding the desired product 10 as a cream solid, 654 mg (76%).

[4] has NMR (CDCl₃; 250 MHz) δ 1.70 (m, 1H), 1.75 (d, 1H), 2.63-2.77

25 (m, 1H), 3.15-3.50 (m, 3H), 3.90-4.00 (m, 1H), 4.05 (s, 3H), 4.07-4.23 (m, 2H), 4.63 (m, 2H), 5.23-5.37 (m, 2H), 5.85-6.03 (m, 1H), 8.22 (d, 1H), 8.35 (dd, 1H), 8.95 (s(br), 1H), 9.20 (s, 1H).

MS (FAB) m/z 380 (M+H)⁺

Anal. C₁₇H₂₁N₃O₅S. 0.33 C₂HF₃O₂ 417: C 50.9 (50.8), H 5.3 (5.1), N 10.1 (10.1).

30

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Starting material (10(c)) was prepared as follows. Pyridine 2,5-dicarboxylic acid 2-methyl ester (10(a)) (9.0 g; 0.05 mole) was added to stirring thionyl chloride (25 mL) and the mixture refluxed gently for 2.5 hours. The excess thionyl chloride was removed in vacuo and the residual solid azeotrope with toluene (2 x 25 mL) to give

5 5-chlorocarbonyl-pyridine-2-carboxylic acid methyl ester (10(b)) which was used crude in the next reaction.

To a stirring solution of compound (15(b)) (Example 15) (220 mg; 0.7 mmole) in acetonitrile (6 mL) was added a solution of (10(b)) (0.7 mmole) in acetonitrile (4 mL). Triethylamine (0.29 mL; 2.1 mmole) was added and the solution stirred for 23 hours. The

10 solvent and excess triethylamine were removed in vacuo and the residue partitioned between chloroform and water. The organic phase was washed with water, aqueous sodium hydrogen carbonate solution and brine, dried over magnesium sulphate and taken to dryness. The residual orange gum was flash chromatographed on kieselgel 9385, eluting initially with iso-hexane then with increasing proportions of ethyl acetate. The desired

15 starting material 10(c) was isolated as a white foam (200 mg; 60%).

NMR (CDCl₃; 250 MHz) 1.50 (s, 9H), 1.80 (m, 1H), 2.62-2.75 (m, 1H), 3.30-3.37 (m, 1H), 3.39-3.50 (m, 1H), 3.68-3.80 (m, 1H), 3.83-3.95 (m, 1H), 4.03 (s, 3H), 4.13-4.28 (m, 2H), 4.62 (m, 2H), 5.20-5.37 (m, 2H), 5.87-6.02 (m, 1H), 8.2 (d, 1H), 8.3 (dd, 1H), 8.87 (s, 1H), 9.2 (s, 1H).

20 MS (FAB) m/z 480 (M+H)

Anal. C₂₂H₂₉N₃O₇S 479 : C 55.1 (55.1), H 6.4 (6.1), N 8.5 (8.8).

Example 11 (see Scheme 11)

(2S,4S)-2-[[[(5-ethoxycarbonyl-thiophene-2-carbonyl)-amino]-methyl]-4-sulfanyl-pyrrolidine-1-carboxylic acid allyl ester

25

TFA (2mL; 26 mmole) was added to a stirring solution of (2S,4S)-2-[[[(5-ethoxycarbonyl-thiophene-2-carbonyl)-amino]-methyl]-4-BOCsulfanyl-pyrrolidine-1-carboxylic acid allyl ester (11(b)) (130mg ; 0.26 mmole) in

30 dichloromethane (20 mL). The solution was stirred under argon for 19 hours. The solvent

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and excess TFA were removed in vacuo and the residue dried under high vacuum to give the desired product 11 as a water-white gum (64%).

NMR (CDCl₃; 250 MHz) δ 1.38 (t, 3H), 1.55-1.70 (m, 1H), 1.75(d, 1H), 2.60-2.76 (m, 1H), 3.10-3.50 (m, 3H), 3.80-3.95 (m, 1H), 4.05-4.25 (m, 2H), 4.38 (q, 2H), 4.70 (m, 2H),

5 5.20-5.40 (m, 2H), 5.85-6.05 (m, 1H), 7.47 (d, 1H), 7.73 (d, 1H), 8.52 (s(br), 1H)

MS (FAB) m/z 399 (M+H)⁺ Anal. C₁₇H₂₂N₂O₅S₂ 0.5 C₂HF₃ O₂ 455:

C 47.6 (47.5), H 5.2 (4.9), N 6.1 (6.15).

Starting material 11(b) was prepared in an analogous manner to the equivalent
10 step in Example 10 but with addition of 5-chlorocarbonyl-thiophene-2-carboxylic
-acid-ethyl-ester (11(a)) to compound (15(b)) (Example 15) with similar chromatographic
work up. 11(b) is a tacky water white gum. Yield 60%. Preparation of (11(a)) is described
in Journal of the American Pharmaceutical Association (Sci. Ed.) Vol. 41 pp 273-276
(1952).

15 NMR of 11(b): (CDCl₃; 250 MHz) δ 1.4 (t, 3H), 1.5 (s, 9H), 1.70-1.85 (m, 1H), 2.57-2.73
(m, 1H), 3.26-3.36 (m, 1H), 3.38-3.50 (m, 1H), 3.65-3.87 (m, 2H), 4.10-4.25 (m, 2H), 4.35
(q, 2H), 4.65 (m, 2H), 5.20-5.38 (m, 2H), 5.85-6.04 (m, 1H), 7.47 (d, 1H), 7.72 (d, 1H),
8.45 (s(br), 1H).

MS (FAB) m/z 499 (M+H)⁺, other m/z 183

20 Anal. C₂₂H₃₀N₂O₇S₂ 498 C 53.4 (53.0), H 6.3 (6.1), N 5.5 (5.6)

Example 12 (see Scheme 12)

N-(3,4-dichlorobenzyl)-N'-((2S,4S),4-sulfanyl-pyrrolidin-2-yl-methyl) thiophene-2,5-dicarboxamide

25 To a stirring solution of N-(3,4-dichlorobenzyl)-N'-((2S,4S),-
1-allyloxycarbonyl-4-sulfanyl-pyrrolidin-2-yl-methyl) thiophene-2,5-dicarboxamide
(12(e)) (59 mg; 0.1 mmole) in dichloromethane (10 mL), under argon, was added
trimethylsilyliodide (0.35 mL; 0.25 mmole). After 20 hours at ambient temperature the
dichloromethane and excess trimethylsilyliodide were removed in vacuo and the residue
30 treated with methanol (3 mL). The insoluble material was treated with further methanol (2

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x 3 mL) and then triturated with diethyl ether to yield a solid which was filtered and dried to give the desired product 12 as a light brown solid (59%).

NMR (DMSO- d_6 ; 250 MHz) δ 1.65-1.90 (m, 1H), 2.50-2.62 (m, 1H), 3.20-3.40 (m, 2H), 3.55-3.70 (m, 2H), 3.75-3.90 (m, 2H), 4.45 (d, 2H), 7.32 (m, 1H), 7.58 (m, 2H), 7.73 (d, 1H), 7.78 (d, 1H), 8.68 (br, 1H), 8.88 (t, 1H), 9.22 (t, 1H).
MS (FAB) m/z 444 (M+H)⁺ other 111, 312 Anal. C₁₈H₁₉Cl₂N₃O₂S₂ 1.25 HI 0.5 C₄H₁₀O 640 C 37.6 (37.5), H 3.5 (3.9), N 6.5 (6.6).

Starting material (12(e)) was prepared as follows. To a stirring solution of 3,4-dichlorobenzylamine (0.53 mL; 4.0 mmole) in acetonitrile (10 mL) was added triethylamine (1.67 mL; 12.0 mmole) and a solution of (11(a)) (0.87g; 4.0 mmole, see Example 11) in acetonitrile (20 mL). The solution was stirred at ambient temperature, under argon, for 22 hours. The solvent and excess triethylamine were removed in vacuo and the residue partitioned between chloroform and water. The organic phase was washed with water and brine, dried over magnesium sulphate and vacuumed to dryness to give 5-(3,4-dichlorobenzyl-carbamoyl)-thiophene-2-carboxylic acid ethyl ester (12(a)) as a cream solid (90%).

NMR (CDCl₃; 250 MHz) δ 1.40 (t, 3H), 4.38 (q, 2H), 4.57 (d, 2H), 6.47 (t(br), 1H), 7.28 (m, 1H), 7.42 (m, 2H), 7.48 (d, 1H), 7.73 (d, 1H) MS (CI) m/z 358 (M+H)⁺
Anal. C₁₅H₁₃Cl₂NO₃S 358: C 50.4 (50.3), H 3.8 (3.7), N 3.9 (3.9).

Aqueous 1M sodium hydroxide (16.3 mL; 16.3 mmole) was added to a stirring solution of (12(a)) (1.17g; 3.3 mmole) in ethanol (70 mL). The reaction mixture was stirred at ambient temperature for 19 hours, reduced to a small volume, diluted with water and adjusted to pH 2 by addition of 2M hydrochloric acid. The filtered solid was washed with water and dried in vacuo to give 5-(3,4-dichlorobenzyl-carbamoyl)-thiophene-2-carboxylic acid (12(b)) as a white solid (83%).

NMR (DMSO d_6 ; 200MHz) δ 4.43 (d, 2H), 7.3 (dd, 1H), 7.58 (m, 2H), 7.68 (d, 1H), 7.78 (d, 1H), 9.28 (t, 1H) MS (CI) m/z 330 (M+H)⁺
Anal. C₁₃H₉Cl₂NO₃S 330 C 47.3 (47.3), H 2.7 (2.7), N 4.2 (4.2).

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A stirring solution of (12(b)) (495mg; 1.5 mmole) in dichloromethane (25 mL) was cooled in an ice bath and DMF (1 drop) and oxalyl chloride (0.175 mL ; 2.0 mmole) added dropwise. The solution was stirred at ambient temperature under argon for 4 hours. The dichloromethane and excess oxalyl chloride were removed in vacuo. The residue was
 5 azeotroped with toluene (2 x 15 mL) to give 5-(3,4-dichlorobenzyl-carbamoyl)-thiophene-2-carbonyl-chloride (12(c)) which was used crude in the next step.

Triethylamine (0.83 mL; 4.5 mmole) and a solution of compound (15(b)) (Example 15) (316 mg; 1.0 mmole) in acetonitrile (10 mL) were added to a stirring mixture of (12(c)) (1.5 mmole) in acetonitrile (15 mL) and stirred at ambient temperature under
 10 argon for 19 hours. The acetonitrile and excess triethylamine were removed in vacuo and the residue partitioned between chloroform and water. The organic phase was washed with water and brine, dried over magnesium sulphate and vacuumed to dryness to give N-(3,4-dichlorobenzyl)-N'-((2S,4S),-1-allyloxycarbonyl-4-BOCsulfanyl-pyrrolidin-2-yl-methyl) thiophene-2,5-dicarboxamide (12(d)) as a tacky
 15 brown solid (95%).

NMR (CDCl₃; 200 MHz) δ 1.5 (s, 9H), 1.65-1.85 (m, 1H), 2.47-2.73 (m, 1H), 3.25-3.50 (m, 2H), 3.65-3.85 (m, 2H), 4.10-4.23 (m, 2H), 4.57 (d, 2H), 4.64 (m, 2H), 5.20-5.40 (m, 2H), 5.85-6.05 (m, 1H), 6.45 (t, 1H), 7.20 (dd, 1H), 7.40 (m, 2H), 7.46 (d, 1H), 7.53 (d, 1H), 8.47 (br, 1H) MS (FAB) m/z 628 (M+H)⁺ Anal. C₂₇H₃₁Cl₂N₃O₆S.H₂O
 20 646 C 50.2 (50.2), H 4.9 (5.1), N 6.5 (6.5).

TFA (5 mL; 65 mmole) was added to a stirred solution of (12(d)) (600 mg; 0.93 mmole) in dichloromethane (25 mL). The solution was stirred at ambient temperature under argon for 4 hours, solvent and excess TFA were removed in vacuo and the residue
 25 azeotroped with toluene to give the desired starting material (12(e)).

NMR (CDCl₃; 250 MHz) δ 1.55-1.75 (m, 1H), 1.75 (d, 1H), 2.50 - 2.72 (m, 1H), 3.12-3.43 (m, 1H), 3.65-3.90 (m, 2H), 4.03-4.20 (m, 2H), 4.54 (d, 2H), 4.63 (m, 2H), 5.17-5.37 (m, 2H), 5.85-6.03 (m, 1H), 6.63 (br, 1H), 7.10-7.55 (m, 5H), 8.5 (br, 2H)
 MS (FAB) m/z 528 (M+H)⁺ Anal. C₂₂H₂₃Cl₂N₃O₄S₂ 0.33 C₄H₁₀O 0.3 C₂HF₃O₂
 30 586.5 C 49.0 (49.0), H 4.5 (4.6), N 7.2 (7.2).

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Example 13 (see Scheme 13)

5-[N-(3,4-dichlorobenzyl)carbamoyl]-N-((2S,4S)-4-sulfanylpyrrolidin-2-yl-methyl)pyridine-2-carboxamide

5 5-[N-(3,4-dichlorobenzyl)carbamoyl]-N-((2S,4S)-1-allyloxycarbonyl-4-sulfanylpyrrolidin-2-yl-methyl)pyridine-2-carboxamide (13(e)) was treated with trimethylsilyliodide in similar manner to compound (12(e)) in Example 12. The desired product 13 was obtained as a medium brown solid (26%).

NMR (DMSO-d₆; 200 MHz) δ 1.70-1.82 (m, 1H), 3.15-3.40 (m, 2H), 3.55-3.90 (m, ?H),
10 4.52 (d, 2H), 7.35 (dd, 1H), 7.60 (m, 2H), 8.18 (d, 1H), 8.47 (dd, 1H), 8.75 (br, 1H), 9.10 (d, 1H), 9.28 (t + ? 2H), 9.42 (t, 1H).

MS (FAB) m/z 439 (M+H)⁺. Anal. C₁₉H₂₀Cl₂N₄O₂S. 1.5 H₂O. 0.33 C₄H₁₀O 655.7
C 37.4 (37.2), H 3.4 (3.7), N 8.1 (8.5).

15 Starting material (13(e)) was prepared as follows. 5-chlorocarbonyl-pyridine-2-carboxylic acid methyl ester was reacted with 3,4-dichlorobenzylamine analogously with preparation of compound (12(a)) in Example 12 to obtain 5(3,4-dichlorobenzylcarbamoyl)-pyridine-2-carboxylic acid methyl-ester (13(a)) as a cream solid (61%).

NMR (CDCl₃; 250 MHz), δ 4.05 (s, 3H), 4.62 (d, 2H), 6.80 (t(br), 1H), 7.22 (dd, 1H), 7.43
20 (m, 2H), 8.20 (d, 1H), 8.30 (m, 1H), 9.08 (d, 1H). MS (CI) m/z 339 (M+H)⁺
Anal. C₁₅H₁₂Cl₂N₂O₃ 339 C 53.2 (53.1), H 3.5 (3.6), N 8.1 (8.3).

Compound (13(a)) was treated in an analogous manner to compound (12(a)) in Example 12 to obtain 5(3,4-dichlorobenzylcarbamoyl)-pyridine-2-carboxylic acid (13(b))
25 as an off-white solid (82%).

NMR (DMSO-d₆; 200MHz) δ 4.50 (d, 2H), 7.33 (dd, 1H), 7.58 (m, 2H), 8.13 (d, 1H), 8.37 (dd, 1H), 9.12 (d, 1H), 9.40 (t, 1H) MS (CI) m/z 325 (M+H)⁺
Anal. C₁₄H₁₀Cl₂N₂O₃. H₂O 343 C 48.9 (48.9), H 3.5 (3.5), N 8.0 (8.2).

Compound (13(b)) was treated in an analogous manner to compound (12(b))
30 in Example 12 to give 5(3,4-dichlorobenzylcarbamoyl)-pyridine-2-carbonylchloride (13(c)) which was used crude in the next reaction.

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Compound (13(c)) was reacted with compound (15(b)) (Example 15) in a similar manner to compound (12(c)) in Example 12 to give 5-[N-(3,4-dichlorobenzyl)carbamoyl]-N-((2S,4S)-1-allyloxycarbonyl-4-BOCsulfanylpyrrolidin-2-yl-methyl)pyridine-2-carboxamide as a light brown solid (13(d)) (81%).

5 NMR (CDCl₃; 250 MHz) δ 1.50 (s, 9H), 1.73-1.90 (m, 1H), 2.50-2.65 (m, 1H), 3.20-3.30 (m, 1H), 3.62-3.80 (m, 2H), 4.10-4.27 (m, 2H), 4.65 (d?, 4H), 5.18-5.38 (m, 2H), 5.83-6.05 (m, 1H), 6.80 (t(br), 1H), 7.20-7.28 (m, 2H), 7.40-7.48 (m, 2H), 8.23 (s, 2H), 8.75 (br, 1H), 8.98 (d?, 1H).

MS (FAB) m/z 623 (M+H)⁺ Anal. C₂₈H₃₂Cl₂N₄O₆S 623 C 53.8 (53.9), H 5.1 (5.2), N 10 8.9 (9.0) mp 136-137.5°C.

Compound (13(d)) was treated in a similar manner to compound (12(d)) in Example 12 to give the desired starting material (13(e)) as a light brown solid (64%).

NMR (CDCl₃; 250 MHz) δ 1.70 (d, 1H), 1.80-2.00 (m, 1H), 2.52-2.65 (m, 1H), 3.05-3.25 15 (m, 2H), 3.60-3.85 (m, 2H), 4.05-4.20 (m, 2H), 4.60 (d?, 4H), 5.18-5.33 (m, 2H), 5.85-6.03 (m, 1H), 6.80 (br, 1H), 7.20 (dd, 1H), 7.40-7.47 (m, 2H), 8.23 (s, 2H), 8.78 (br, 1H), 9.0 (s, 1H). MS (FAB) m/z 523 (M+H)⁺

Anal. C₂₃H₂₄Cl₂N₄O₄S. 0.1 C₂HF₃O₂ 534.4

C 52.4 (52.1), H 4.6 (4.5), n 10.3 (10.5) mp 101 -105°C

20

Example 14 (see Scheme 14)

1-hydroxy-4-(((2S,4S),4-sulfanyl-pyrrolidin-2-yl-methyl)-amino-sulfonyl)naphthalene-2-carboxylic-acid

25 To a stirring solution of 1-hydroxy-4-(((2S,4S),1-allyloxycarbonyl-4-sulfanyl-pyrrolidin-2-yl-methyl)-aminosulfonyl]-naphthalene-2-carboxylic-acid (14(c)) (47.5 mg; 0.1 mmole) in dichloromethane (10 mL) was added TMSI (0.56 mL; 0.4 mmole). The solvent and excess TMSI were removed in vacuo after 6 hours. Methanol (5 mL) was added to the residue 30 and then removed in vacuo from the solution. The residue was triturated with diethyl ether, filtered and dried in vacuo to obtain the desired product 14 as a brown solid (74%).

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NMR (DMSO-d₆; 250 MHz) δ 1.45-1.62 (m, 1H), 2.25-2.45 (m, 1H), 2.90-3.25 (m, 3H), 3.45-3.70 (m, 2H), 7.72 (m, 1H), 7.85 (m, 1H), 8.12 (m, 1H), 8.38-8.60 (m, 2H), 9.15 (br, 1H)

MS (FAB) m/z 383 (M+H)⁺

5 Anal. C₁₆H₁₈N₂O₅S₂. 1.25 H₂O. 0.5 C₄H₁₀O 579 C 37.0 (37.3), H 4.1 (4.2), N 4.8 (4.8).

Starting material (14(c)) was prepared as follows. Compound (15(b)) (Example 15) and 1-hydroxy-4-chlorosulfonyl-naphthalene-2-carboxylic acid (14(a)) were coupled in a similar manner to the equivalent step in Example 15 to give

10 1-hydroxy-4-(((2S,4S), 1-allyloxycarbonyl-4-BOCsulfonyl-pyrrolidin-2-yl-methyl)-aminosulfonyl]-naphthalene-2-carboxylic-acid (14(b)) as a light brown solid (80%).

NMR (CDCl₃; 250 MHz) δ 1.45 (s, 9H), 1.50-1.75 (m, 1H), 2.28-2.42 (m, 1H), 2.96-3.10 (m, 2H), 3.48-3.60 (m, 1H), 3.80-3.90 (m, 1H), 3.95-4.05 (m, 1H), 4.47 (m, 2H), 4.53-4.63 (m, 1H), 7.55 (m, 1H), 7.67 (m, 1H), 8.50 (m, 2H), 8.70 (m, 1H) MS (FAB) M+Na⁺ 589, other 317, 261 Anal. C₂₅H₃₀N₂O₉S₂.H₂O.0.8 C₃H₁₅N 664.8 C 53.7 (53.8), H 6.7 (6.6), N 5.9 (5.9).

2M Aqueous sodium hydroxide (5 mL: 10.0 mmole) was added to a stirring solution of (14(b)) (333mg; 0.5 mmole) in methanol (5 mL). The solution was evaporated to dryness after 42 hours and the residue dissolved in water (10 mL). The solution was adjusted to pH 2 with 2M hydrochloric acid and the solid was filtered, washed with water and dried in vacuo to give the desired starting material (14(c)) as a white solid (72%).

NMR (CDCl₃; 200 MHz) δ 1.48-1.70 (m, 2H), 2.38-2.52 (m, 1H), 2.85-3.40 (m, ?H), 3.90-4.05 (m, 2H), 4.40-4.60 (m, 3H), 5.10-5.35 (m, 3H), 5.70-5.95 (m, 2H), 6.20-6.45 (br, 1H), 7.57-7.90 (m, 3H), 8.43-8.70 (m, 4H)

MS (FAB) m/z 467 (M+H)⁺ Anal. C₂₀H₂₂N₂O₇S₂. 0.5 H₂O 475 C 50.6 (50.5), H 4.8 (4.8), N 6.0 (5.9).

30

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Example 15 (see Scheme 15)

(2S)-2-{3-[(2S,4S)-4-sulfanyl-pyrrolidin-2-yl-methyl)-sulfamoyl]-benzoylamino}-4-methylsulfanyl-butyric acid methyl ester

- 5 TFA (2.0 mL) was added to a stirred solution of (2S)-2-{3-[(2S,4S)-4-BOCsulfanyl-pyrrolidin-2-yl-methyl)-sulfamoyl]-benzoylamino}-4-methylsulfanyl-butyric acid methyl ester (15(d)) (101 mg, 0.18 mmol) in CH₂Cl₂ (2.0 mL) at room temperature under argon. After 1 h the reaction mixture was concentrated to a dryness, azeotroped with toluene (3 x 10 mL) and dried to yield the
- 10 desired product 15 as a colourless gum: 101.8 mg (99%).
- ¹H NMR (CDCl₃, 250MHz) δ 1.6-1.8 (1H, m); 2.0 (1H, d, SH); 2.1-2.4 (5H, m); 2.52.65 (3H, m); 3.15-3.4 (3H, m) 3.45-3.65 (1H, m); 3.7-3.85 (4H, m) 3.9-4.1 (1H, m); 4.85-5.0 (1H, m); 7.55-7.7 (2H, m) 7.8 (1H, s); 8.0 (1H, d); 8.1 (1H, d); 8.3 (1H, s); 9.0-9.4 (1H, s); 10.0-10.4 (1H, s).
- 15 MS (ESP+) m/z 462 (M+H)⁺.

- Starting material (15(d)) was prepared as follows. Triethylamine (3.0mL, 21.5mmol) was added to a stirred suspension of L-methionine methyl ester. HCl(4.37 g, 21.8 mmol) in CH₂Cl₂ (50 mL). The resulting mixture was left to stir for 30 min at room
- 20 temperature then filtered. The filtrates were then added to a stirred solution of 3-chlorosulphonyl-benzoyl chloride (5.23 g, 21.9 mmol) and triethylamine (7.6 mL, 54.7 mmol) in CH₂Cl₂ (50 mL) at 0° under argon. The reaction mixture was allowed to warm to room temperature and quenched with ice-water(100 mL). The organics were the dried over MgSO₄, filtered and concentrated to a viscous brown gum. This was then purified by
- 25 flash chromatography on 9385 SiO₂, eluting with 50% EtOAc/i-Hexane to give (2S)-2-(3-chlorosulfonyl-benzoylamino)-4-methylsulfonyl-butyric acid methyl ester (15(a)) as a viscous orange oil: 2.88 g (36%).

- ¹H NMR (CDCl₃, 250 MHz) δ 2.1-2.2 (5H, m); 2.65 (2H, t); 3.83 (3H, s); 4.95 (1H, m); 7.23 (1H, d); 7.74 (1H, t); 8.2 (2H, m); 8.47 (1H, m). MS (CI) m/z 366 (M+H)⁺, 332, 300.
- 30 A solution of 15(a) (1.53 g, 4.18 mmol) in CH₂Cl₂ (20 mL) was added to a stirred solution of

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- (2S,4S)-2-aminomethyl-4-BOCsulfanyl-pyrrolidine-1-carboxylic acid allyl ester (15(b)) (prepared as described in International Patent Application WO 92/17480, see pages 39-41) (1.32g, 4.18 mmol) and (iPr)₂NEt (1.5 mL, 9.0 mmol) in CH₂Cl₂ (30mL) at 0°C under argon. The resulting solution was allowed to warm to room temperature and stirred for 18
- 5 hours. The reaction mixture was then washed with water (100 mL), dried over MgSO₄, filtered and concentrated to a viscous white gum. This was then purified by flash chromatography on 9385 SiO₂, eluting with a gradient of 35-50% EtOAc/i-Hexane to give (2S,4S)-4-BOCsulfanyl-2-{[3-([1S]-1-methoxycarbonyl-3-methylsulfanyl-propylcarbamoyl)-benzenesulfonylamino]-methyl}-pyrrolidine-1-
- 10 carboxylic acid allyl ester (15(c)) as a colourless foam: 2.19 g (81.3%).
- ¹H NMR (CDCl₃, 200MHz) δ 1.5 (9H, s); 1.65-1.9 (1H, s); 2.05-2.35 (5H, m); 2.4-2.7 (3H, m); 3.3-3.4 (3H, m); 3.55-3.75 (1H, m); 3.8 (3H, s); 3.9-4.2 (2H, m); 4.55 (2H, d); 4.98 (1H, m); 5.15-5.35 (2H, m); 5.8-6.0 (1H, m); 6.5 (1H, s); 7.4 (1H, s); 7.55 (1H, t); 7.9-8.05 (2H, m); 8.25 (1H, m).
- 15 MS (FAB) m/z 646 (M+H)⁺, 590, 568, 546, 230.
- Anal. Calcd for C₂₇H₃₉N₃O₉S₃·0.3CH₂Cl₂: C, 48.8; H, 5.95; N, 6.26.
- Found C, 48.9; H, 6.2; N, 6.0.

- Tri-nButyl tin hydride (565 mL, 2.1 mmol) was added to a stirred solution of
- 20 (15(c)) (1.18 g, 1.8 mmol) and (PPh)₃PdCl₂ (13 mg, 0.018 mmol) in a mixture of water (0.5 mL) and CH₂Cl₂ (100 mL). The reaction mixture was left to stir for 10 minutes, dried over MgSO₄, filtered and concentrated to a brown oil. This was then purified by flash chromatography on 9385 SiO₂, eluting with a gradient of 0-10% EtOAc/i-Hexane to give the desired starting material 15(d) as a white foam: 751 mg (73%).
- 25 ¹H NMR (CDCl₃+CD₃COOD, 250MHz) δ 1.5 (9H, s); 1.85-1.97 (1H, m); 2.1-2.35 (5H, m); 2.45-2.7 (3H, m); 3.1-3.4 (3H, m); 3.65-4.25 (6H, m); 4.9-5.0 (1H, m); 7.63 (1H, t); 7.97-8.05 (1H, m); 8.1-8.17 (1H, m); 8.35-8.42 (1H, m).
- MS (ESP+) m/z 562 (M+H)⁺, 462.
- Anal. Calcd for C₂₃H₃₅N₃O₇S₃: C, 49.2; H, 6.28; N, 7.48.
- 30 Found C, 49.4; H, 6.3; N, 7.2.

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Example 16 (see Scheme 16)

(2S),2-{3-[(2S,4S)-4-sulfanyl-pyrrolidin-2-yl-methyl]-sulfamoyl}-benzoylamino}-4-methylsulfanyl-butyric acid

5 2N NaOH(2.0 mL, 4.0 mmol) was added to a stirred solution of compound (15(d)) (prepared in Example 15) (200 mg, 0.36 mmol) in MeOH at room temperature under argon. After 18 h the reaction mixture was concentrated to remove the MeOH. The resulting residues were dissolved in H₂O(2.0 mL) and acidified to pH3 with 2N HCl. The resulting solution was purified by reverse phase HPLC (Dynamax C18.8μ prepcolumn),
10 eluting with a gradient of 0-40% MeOH/H₂O. Product fractions were concentrated and azeotroped with toluene (3 x 25 mL) to give a colourless glass which was then triturated with Et₂O (25 mL), filtered and dried to yield the desired product 16 as a white powder: 85.2 mg (54%).

¹H NMR (DMSO-D₆+CD₃COOD,250 MHz) δ1.45-1.65 (1H, m); 2.0-2.2 (5H, m);
15 2.3-2.7 (3H+DMSO, m); 2.95-3.2 (3H, m); 3.35-4.2 (3H, m); 4.5-4.65 (1H, m); 7.65-7.8 (1H, m); 7.9-8.05 (1H, m); 8.1-8.25 (1H, m); 8.3-8.4 (1H, m).

MS (FAB) m/z 448 (M+H)⁺.

Anal. Calcd for C₁₇H₂₅N₃O₅S₃: C, 45.6; H, 5.63; N, 9.39.

Found C. 45.5; H. 5.8; N. 9.1.

20

Example 17 (see Scheme 17)

N-(3,4-dichlorophenyl)-3-[(2S,4S)-4-sulfanyl-pyrrolidin-2-yl-methyl]-sulfamoyl]-benzamide

25 N-(3,4-dichlorobenzyl)-3-[(2S,4S)-4-BOCsulfanyl-pyrrolidin-2-yl-methyl]-sulfamoyl]-benzamide (17(c)) was deprotected with TFA (analogously to compound (15(d)) in Example 15) to give the desired product 17 in 97% yield after trituration with Et₂O.

¹H NMR (CDCl₃,200MHz) δ1.5-1.8 (1H, m); 1.8-2.2 (2H+H₂O,m,SH.NH); 2.5-2.7
30 (1H,m); 3.1-3.35 (3H, m); 3.4-4.1 (3H, m); 4.55 (2H, d); 7.15 (1H, dd); 7.2 (1H, s); 7.32

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(1H, d); 7.4 (1H, d); 7.65 (1H+PPh₃PO, m); 7.9 (1H, m); 8.2 (1H, m); 8.35 (1H, m);
 8.5-9.3 (1H, s, NH); 10.3-10.7 (1H, s, NH).
 MS (ESP+) m/z 474 (M+H)⁺, 279(PPh₃PO)

- 5 Starting material (17(c)) was prepared as follows. 3,4-Dichlorobenzylamine was coupled with 3-Chlorosulphonylbenzoyl chloride (analogously as for compound (15(a)) in Example 15) to give
 3-(3,4-dichloro-benzylcarbamoyl)-benzene-sulfonyl-chloride
 (17(a)) in 28% yield.
- 10 ¹H NMR (CDCl₃, 250MHz) δ 4.6 (2H, d); 6.6 (1H, s, NH); 7.2 (1H, dd), 7.4-7.5 (2H, m); 7.75 (1H, t); 8.15-8.25 (2H, m); 8.4 (1H, m) MS (FAB) m/z 378 (M+H)⁺, 380.

- Compound 15(b) (Example 15) was coupled with (17(a)) analogously as for the equivalent step in Example 15 to give
- 15 N-(3,4-dichlorobenzyl)-3-[[[2S,4S],4-BOCsulfanyl-pyrrolidin-2-yl-methyl)-sulfamoyl]-benzamide (17(b)) in 72.5% yield.
- ¹H NMR (CDCl₃, 200MHz) δ 1.5 (9H, s); 1.6-1.9 (1H+H₂O, m); 2.4-2.6 (1H, m); 3.1-3.3 (3H, m); 3.6-3.7 (1H, m); 3.8-4.1 (2H, m); 4.4 (2H, d); 4.6 (2H, d); 5.1-5.3 (2H, m); 5.7-5.95 (1H, m); 6.08 (1H, s, NH); 7.2 (1H, dd); 7.35-7.7 (4H, m); 7.95 (1H, d); 8.15 (1H, d); 8.25-8.35 (1H, s, NH).
- 20 MS (FAB) m/z 658 (M+H)⁺
 Anal. Calcd for C₂₈H₃₃N₃Cl₂O₇S₂: C, 51.1; H, 5.05; N, 6.38.
 Found C, 50.8; H, 5.2; N, 6.2.

- 25 Compound (17(b)) was deprotected, analogously as for the equivalent step in Example 15, to give the desired starting material (17(c)) in 70% yield.
- ¹H NMR (CDCl₃, 250MHz) δ 1.15-1.45 (1H, m); 1.5 (9H, s); 2.25-2.4 (1H, m); 2.6-2.9 (4H, m); 3.02 (1H, dd); 3.25-3.4 (2H, m); 3.45-3.6 (1H, m); 4.6 (2H, m); 7.05 (1H, m); 7.2 (1H, dd); 7.4 (1H, d); 7.45 (1H, d); 7.6 (1H, t); 7.95 (1H, d); 8.1 (1H, d); 8.25 (1H, s).
- 30 MS (ESP+) m/z 574 (M+H)⁺, 574, 279 (PPh₃O)

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Example 18 (see Scheme 18)

N-(3,4-dichlorobenzyl)-N'-([2S,4S],4-sulfanyl-pyrrolidin-2-yl-methyl)-
isophthalamide

- 5 N-(3,4-dichlorobenzyl)-N'-([2S,4S],4-BOCsulfanyl-pyrrolidin-2-yl-methyl)-isophthalamide (18(e)) was deprotected with TFA (analogously to the equivalent step in Example 15) to give the desired product 18 in 100% yield after trituration with Et₂O.
- ¹H NMR (CDCl₃+CD₃COOD, 250MHz) δ 1.75-1.9 (1H, m); 2.6-2.75 (1H, m); 3.2-3.35 (1H, m); 3.45-3.65 (1H, m); 3.7-3.95 (3H, m); 4.05-4.15 (1H, m); 4.6 (2H, s); 7.2 (1H, dd); 7.4 (1H, d); 7.55 (1H, t); 7.95-8.05 (1H, m); 8.1-8.2 (1H, m); 8.4 (1H, m). MS (ESP+) m/z 438 (M+H)⁺.

Starting material (18(e)) was prepared as follows. A suspension of isophthalic acid monomethyl ester (18(a)), (2.65 g, 14.7 mmol) in CH₂Cl₂ (100 mL) and DMF (10 drops) was treated with oxalyl chloride (2.6 ml, 29.8 mmol) at 0° under argon. The reaction mixture was allowed to warm to room temperature over 18h. The resulting solution was concentrated and azeotroped with toluene to give a crystalline yellow solid. This was then redissolved in CH₂Cl₂ (100 mL) and added dropwise to a stirred solution of 3,4-dichlorobenzylamine (2.6 g, 14.7 mmol) and Et₃N (5 mL, 35.9 mmol) in CH₂Cl₂ (100 mL) at 0° under argon. The resulting solution was allowed to warm to room temperature over 4 hours, washed with 1N HCl(50 mL), saturated NaHCO₃ (aq) (50 mL), dried over MgSO₄, filtered and concentrated to an orange oil. This was then purified by flash chromatography on 9385 SiO₂ eluting on a gradient of 25-50% EtOAc/i-Hexane to yield 3-(3,4-dichlorobenzyl-carbamoyl)-benzoic acid methyl ester (18(b)) as a pale yellow oil: 3.99g (80%).

¹H NMR (CDCl₃,200MHz) δ 3.9 (3H, s); 4.6 (2H, d); 6.6-6.8 (1H, t, NH); 7.18 (1H, dd); 7.38-7.45 (2H, m); 7.54 (1H,t); 8.0-8.1 (1H, m); 8.13-8.23 (1H, m); 8.35-8.42 (1H, m). MS (CI) m/z 338 (M+H)⁺.

30

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A stirred solution of (18(b)) (3.85 g, 11.4 mmol) in MeOH (100 mL) at room temperature under argon was treated with 2N NaOH (12 mL, 24 mmol). The reaction mixture was allowed to stir at room temperature for 4 h. concentrated to 1/5 volume and acidified to pH4 with 2N HCl. The resulting precipitate was then collected by filtration.

- 5 washed with water (2 x 25 mL) and dried under high vacuum to yield 3-(3,4-dichlorobenzyl-carbamoyl)-benzoic acid (18(c)) as a white powder: 2.9 g (79%).
¹H NMR (DMSO-D₆, 200MHz) δ4.49 (2H, d); 7.32 (1H, dd); 7.5-7.7 (3H, m); 8.0-8.2 (2H, m); 8.42-8.53 (1H, m); 9.27 (1H, t, NH); 13.0-13.4 (1H, s, COOH).
 MS (ESP+) m/z 324 (M+H)⁺, 159.

- 10 Anal. Calcd for C₁₅H₁₁NO₃Cl₂.0.4H₂O C, 54.4; H, 3.59; N, 4.23
 Found C, 54.0; H, 3.2; N, 4.2

- 1-(3-Dimethylaminopropyl)-3-ethyl carbodiimide.HCl (655 mg, 3.4 mmol) and 1-Hydroxybenztriazole (463 mg, 3.4 mmol) were added portionwise to a stirred
 15 solution of (18(c)) (1.0 g, 3.1 mmol) in DMF (20 mL) at 0° under argon. After 30 mins a solution of compound (15(b)) (Example 15) (1.13 g, 3.57 mmol) in DMF (20 mL) was added dropwise, followed by N-methyl morpholine (375 ml, 3.4 mmol). The mixture was then allowed to warm to room temperature over 4 hours. The resulting reaction mixture was concentrated to 1/5 volume and diluted with EtOAc(100 mL). This solution was then
 20 washed successively with 1N citric acid (100 mL), saturated NaHCO₃(aq) (100 mL), water (100 mL) and brine (100 mL), dried over MgSO₄, filtered and concentrated to a white foam. This was then purified by flash chromatography on 9385 SiO₂, eluting on a gradient of 50-75% EtOAc/i-Hexane to yield (2S,4S)-4-BOCsulfanyl-2-
 {[3-(3,4-dichlorobenzylcarbamoyl)-benzoylamino]-methyl}-pyrrolidine-1-carboxylic acid
 25 allyl ester (18(d)) as a white foam: 1.57 g (82%).
¹H NMR (CDCl₃, 250MHz) δ1.5 (9H, s); 1.6-1.9 (1H, m); 2.55-2.75 (1H, m); 3.2-3.6 (2H,m); 3.65-3.9 (2H, m); 4.1-4.25 (2H, m); 4.5-4.65 (4H, m); 5.15-5.35 (2H, m); 5.38-6.0 (1H, m); 6.87 (1H, t, NH); 7.2 (1H, dd); 7.4 (1H, d); 7.45 (1H, d); 7.55 (1H, t); 7.95 (1H, d); 8.07 (1H, d); 8.25 (1H, s); 8.35-8.6 (1H, s, NH).
 30 MS (ESP+) m/z 622 (M+H)⁺, 566.522.

Anal. Calcd for C₂₉H₃₃N₃Cl₂O₆S : C, 55.9; H, 5.34; N, 6.75

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Found C, 56.1; H, 5.6; N, 6.6

Compound (18(d)) was deprotected (analogously as for the equivalent step in Example 15) to give the desired starting material (18(e)) in 67% yield.

- 5 ^1H NMR (CDCl_3 , 200MHz) δ 1.2-1.6 (10H, m); 2.25-2.55 (2H, m, 1H + 1NH); 2.9 (1H, q); 3.3-3.75 (5H, m); 4.6 (2H, d); 6.9-7.05 (1H, m, NH); 7.05-7.15 (1H, m, NH); 7.2 (1H, dd); 7.4 (1H, d); 7.45 (1H, d); 7.52 (1H, t); 7.9-8.05 (2H, m); 8.23 (1H, m).
MS (ESP+) m/z 538 ($\text{M}+\text{H}$)⁺, 438.

10 Example 19 (see Scheme 19)

(2S,4S),4-sulfanyl-2-[(3-methoxycarbonyl-benzoylamino)-methyl]-pyrrolidin-1-carboxylic acid allyl ester

- (2S,4S),4-BOCsulfanyl-2-[(3-methoxycarbonyl-benzoylamino)-methyl]-pyrrolidin-1-carboxylic acid allyl ester (19(a)), (300 mg, 0.63 mmol) was dissolved in TFA (5 mL) at room temperature under argon. The reaction mixture was concentrated and azeotroped with toluene (3 x 20 mL) to yield the desired product (19) as a colourless viscous gum: 250 mg (105%).

- ^1H NMR (CDCl_3 , 200MHz) δ 1.6-1.85 (2H, m, CH+SH); 2.55-2.85 (2H, m);
20 3.1-3.6 (3H, m); 3.92 (3H, bs); 4.0-4.4 (2H, m); 4.65 (2H, d); 5.15-5.4 (2H, m); 5.8-6.1 (1H, m); 7.53 (1H, t); 8.0-8.1 (1H, m); 8.1-8.25 (1H, m); 8.3-8.7 (2H, m, Aromatic-H + NH).
MS (FAB) m/z 379 ($\text{M}+\text{H}$)⁺, 163.

- 25 Starting material (19(a)) was prepared as follows. A suspension of isophthalic acid monomethyl ester (compound 18(a), Example 18), (2.5 g, 13.89 mmol) in CH_2Cl_2 (50 mL) and DMF (10 drops) was treated with oxallyl chloride (1.35mL, 15.5mmol) at 0° under argon. The reaction mixture was allowed to warm to room temperature over 18 h. The resulting solution was concentrated and azeotroped with toluene to give a crystalline
30 yellow solid. This was then redissolved in CH_2Cl_2 (50mL) and added dropwise to a stirred solution of (2S,4S)-2-aminomethyl-4-BOCsulfanyl-pyrrolidine-1-carboxylic acid

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allyl ester (compound 15(b), Example 15) (2.0 g, 6.33 mmol) and $(i\text{Pr})_2\text{NEt}$ (2.2 mL, 12.66 mmol) in CH_2Cl_2 (50 mL) at 0° under argon. The reaction mixture was allowed to warm to room temperature and stirred for 18 hours, then washed with water (2 x 50 mL), dried over MgSO_4 , filtered and concentrated to a dark brown oil. This was then purified by flash chromatography on 9385 SiO_2 eluting with a gradient of 25-50% EtOAc/i-Hexane to yield the desired starting material (19(a)) as a pale yellow, viscous oil: 1.81 g (60%).

^1H NMR (CDCl_3 , 200 MHz) δ 1.5 (9H, s); 1.65-1.9 (1H, m); 2.55-2.8 (1H, m); 3.3 (1H, q); 3.4-3.65 (1H, m); 3.65-3.9 (2H, m); 3.95 (3H, s); 4.05-4.35 (2H, m); 4.6-4.7 (2H, m); 5.15-5.4 (2H, m); 5.8-6.1 (1H, m); 7.52 (1H, t); 8.02 (1H, dd); 8.15 (1H, dd); 8.25-8.5 (1H, bs, NH);

8.55 (1H, bs). MS (FAB) m/z 479 ($\text{M}+\text{H}^+$), 423, 163.

Anal. Calcd for $\text{C}_{23}\text{H}_{30}\text{N}_2\text{O}_7\text{S}$: C, 57.7; H, 6.32; N, 5.85.

Found C, 57.5; H, 6.4; N, 5.7.

15 Example 20 (see Scheme 20)

N-([2S,4S],4-sulfanyl-pyrrolidin-2-yl-methyl)-3-phenoxy-benzamide

3-Phenoxybenzoic acid was coupled with (2S,4S)-2-aminomethyl-4-BOCsulfanyl-pyrrolidine-1-carboxylic acid allyl ester (compound (15(b)), Example 15), followed by selective deprotection of the N-allyloxycarbonyl group and removal of the BOC group (analogously to the equivalent steps in Example 15) to give the desired product 20.

NMR CDCl_3 δ 1.8 (1H, m), 2.72 (1H, m), 3.01-3.31 (1H, bd), 3.69-3.97 (4H, m), 4.3 (1H, bs), 6.92-7.17 (4.5H, m, aromatics), 7.23-7.45 (5.5H, m, aromatics), 7.56 (1H, m), 7.68 (1H, t), 8.02-8.29 (1H, 2t), 9.02-9.29 (1H, 2bs). +ether.

Analysis requires for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_2\text{S}\cdot\text{HI}$ C=47.33, H=4.6, N=6.13; Found C=47.8, H=4.5, N=6.1

30

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Example 21 (see Scheme 21)

5-([2S,4S],1-allyloxycarbonyl-4-sulfanyl-pyrrolidin-2-yl-methyl)-carbamoyl}-isophthalic acid dimethyl ester

5 Benzene-1,3,5-tricarboxylic acid dimethyl ester was coupled to (2S,4S)-2-aminomethyl-4-BOCsulfanyl-pyrrolidine-1-carboxylic acid allyl ester (compound (15(b)), Example 15), followed by removal of the BOC group (analogously to the equivalent steps in Example 15) to give the desired product 21.

NMR CDCl₃ δ 1.67 (1H, m), 1.75 (1H, d), 2.66-2.89 (3H, m), 3.21

10 (1H, q), 3.27-3.37 (1H, m), 3.5 (1H, m), 3.9 (2H, bs), 3.97 (6H, s), 4.08-4.27 (2H, m), 4.68 (2H, d), 5.2-5.4 (2H, m), 5.88-6.06 (1H, m), 8.68 (2H, bs), 8.8 (1H, d).

Analysis requires for C₂₀H₂₄N₂O₇S C = 55.0 H = 5.54 N = 6.42: Found C = 54.9 H = 5.6 N = 5.75

Example 22 (see Scheme 22)

(2S)-2-{3-([2S,4S]-4-sulfanyl-pyrrolidin-2-yl-methyl)-amino}-benzoyl-amino}-4-methylsulfanyl-butyric acid methyl ester

(2S)-2-{3-([2S,4S]-4-BOCsulfanyl-pyrrolidin-2-yl-methyl)-amino}-

20 benzoylamino}-4-methylsulfanyl-butyric acid methyl ester (22g) was deprotected (analogously as for the equivalent step in Example 15) to yield the desired end product (22).

¹H NMR (CDCl₃+CD₃COOD) δ 1.7-1.9(1H,m); 2.0-2.4(6H+CH₃COOH.M); 2.5-2.8(3h,M); 3.23(1h,Q); 3.45-3.7(2H,m); 3.7-3.9(4H,m); 3.95-4.15(1H,m); 4.8-4.95(1H,m); 6.8(1H,d); 7.0

25 5-7.18(2H,m); 7.23(1H,t).

MS (ESP) m/z 398 (M+H)⁺, 235.

Anal. Calcd for C₁₈H₂₇N₃O₃S₂ 1.25TFA: C, 45.6; H, 5.27; N, 7.78

Found C, 45.2; H, 5.3; N, 7.4

30 Starting material 22g was prepared as follows.

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i) Preparation of (2S,4S),4-BOCsulfanyl-2-formyl-pyrrolidine-1-carboxylic acid allyl ester (22b)

TPAP (5.5mg,0.0156mmol) was added to a stirred mixture of

5 (2S,4S),4-BOCsulfanyl-2-hydroxymethyl-pyrrolidine-1-carboxylic acid allyl ester (22a)(100mg,0.31mmol) and NMM-O (56mg,0.478mmol) in CH₂Cl₂(2.0mL) and CH₃CN (100μL) containing dried powdered 4A° molecular sieve(200mg). The reaction mixture was left to stir for 1h then concentrated to dryness. This was then purified by flash chromatography on SiO₂ (Varian Mega Bond Elut Column) eluting with 50%

10 EtOAc/i-Hexane to give compound 22b as a colourless gum: 66.3mg(66.7%).

¹H NMR (CDCl₃,250MHz) δ1.4-1.6(9H,m);2.0-2.25(1H,m);2.45-2.75(1H,m); 3.45-3.6(1H,m);3.75-3.9(1H,m);3.9-4.1(1H,m);4.1-4.35(1H,m);4.5-4.7(2H,m);5.15-5.4(2H,m);5.75-6.05(1H,m);9.4(1H,s,CHO).

MS (CI) m/z 316 (M+H)⁺,260.216.

15

ii) Preparation of

(2S),2-[(3-amino-benzoyl)-amino]-4-methylsulfanyl-butyric acid methyl ester (22e)

3-Nitro-benzoic acid (22c)(2.0g,11.9mmol) was coupled with L-methionine methyl ester hydrochloride (2.6g,13mmol) according to the method used to synthesise compound 18a. to give

(2S),2-[(3-nitro-benzoyl)-amino]-4-methylsulfanyl-butyric acid methyl ester (22d) as a white solid:3.15g(93.4%)

¹H NMR (CDCl₃,200MHz) δ2.05-2.45(5H,m);2.63(2H,t);3.82(3H,s);4.96(1H,m); 7.2(1H,d,NH);7.65,1H,t);8.18(1H,m);8.39(1H,m);8.65(1H,m).

25 MS (ESP) m/z 313 (M+H)⁺,265,253.

Anal. Calcd for C₁₃H₁₆N₂O₅S:C,50.0;H,5.16;N,8.97

Found C,50.3;H,5.1;N,8.9

Found C,50.3;H,5.1;N,8.9

30 A stirred solution of 22d (500mg,1.62mmol) in MeOH(10mL) was treated portionwise with decolourising charcoal (50mg), and iron III chloride hexahydrate

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(7mg, 0.026mmol). *N,N*-Dimethyl hydrazine (1.5mL, 19.8mmol) was then added dropwise and the resulting suspension was heated to reflux for a total of 18h. The reaction mixture was then concentrated to dryness and the residues purified by flash chromatography on SiO₂ (Varian Mega Bond Elut Column) eluting with 50%EtOAc/i-Hexane. Product

- 5 fractions were then concentrated to yield a colourless oil which crystallised on standing. This was then triturated with Et₂O to give 22e as a white powder which was collected by filtration and dried: 367mg (81.2%)

¹H NMR (CDCl₃, 250MHz) δ 2.0-2.4(5H, m); 2.5-2.65(2H, m); 3.8(3H, s); 4.9(1H, m); 6.75-6.95(2H, m, ArH+CONH); 7.05-7.3(3H, m).

- 10 MS (ESP) m/z 283 (M+H)⁺, 251, 235, 223.

Anal. Calcd for C₁₃H₁₈N₂O₃S: C.55.3; H.6.43; N.9.92

Found C.55.5; H.6.6; N.9.8

iii) Preparation of 22g

- 15 A solution containing 22e (50mg, 0.17mmol) and 22b (54mg, 0.17mmol) in EtOH(2.5mL) was treated with powdered 4A° molecular sieves (100mg) and the resulting suspension was stirred at room temperature for 1h. Acetic acid (10μL) and sodium cyanoborohydride (17mg, 0.27mmol) were then added and the reaction mixture was left to stir for 18h at room temperature. The reaction mixture was then partitioned between
- 20 EtOAc(50mL) and saturated NaHCO₃(aq)(50mL). The aqueous phase was then washed with EtOAc(50mL) and the combined organics dried over MgSO₄, filtered and concentrated to a colourless gum. This was then purified by flash chromatography on SiO₂ (Varian Mega Bond Elut Column) eluting a gradient of 25-40% EtOAc/i-Hexane to give

- 25 (2S)-2-{3-[[[2S,4S]-1-allyloxycarbonyl-4-BOCsulfanyl-pyrrolidin-2-yl-methyl]-amino]-benzoyl-amino}-4-methylsulfanyl-butyric acid methyl ester (22f) as a colourless gum: 60.1mg (60.3%).

¹H NMR (CDCl₃, 200MHz) δ 1.45(9H, s, ^tBu); 1.7-1.9(1H, m); 2.0-2.4(5H, m);

2.45-2.7(3H, m); 3.1-3.35(2H, m); 3.4-3.6(1H, m); 3.6-3.85(4H, m); 4.0-4.3(2H, m);

- 30 4.6(2H, m); 4.8-4.95 (1H, m); 5.15-5.4(2H, m); 5.8-6.1(1H, m); 6.75(1H, d); 6.5-7.3(5H, m).

MS (ESP) m/z 582 (M+H)⁺, 482.

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Compound 22f was deprotected (analogously as for the equivalent step in Example 15) to give the desired starting material 22g in 64% yield.

¹H NMR (CDCl₃+D₂O) δ 1.15-1.95 (10H, m); 1.95-2.15(4H, m, SMe+H);
2.15-2.35(1H, m); 2.35-2.5(1H, m); 2.55(2H, t); 2.75-2.95(1H, m); 2.95-3.15(1H, m);
5 3.15-3.55(3H, m); 3.55-3.7(1H, m); 3.78(3H, s, COMe); 4.9(1H, m); 6.73(1H, m);
6.98-7.13(2H, m); 7.2(1H, t).

MS (ESP) m/z 498 (M+H)⁺.398.

Anal. Calcd for C₂₃H₃₅N₃O₅S₂O.35CH₂Cl₂: C, 53.2; H, 6.82; N, 7.97

Found C, 53.5; H, 7.1; N, 7.5

10

Example 23 (see Scheme 30)

Preparation of

N-((2S,4S)-4-sulfanyl-pyrrolidin-2-ylmethyl)-3-methyl-N-(2-naphthalen-1-yl-ethyl)butyramide (compound 9);

- 15 (2S,4S)-2-[[[(3-Methoxypropyl)-(2-naphthalen-1-ylethyl)amino]methyl]-pyrrolidine-4-thiol (compound 10) and;
(2S,4S)-2-[[[(2-(4-Methoxyphenyl)methyl)-(2-naphthalen-1-ylethyl)amino]methyl]-pyrrolidine-4-thiol (compound 11).

20 Preparation of Compound 9

A solution of starting material N-((2S,4S)-4-BOCsulfanyl-pyrrolidin-2-ylmethyl)-3-methyl-N-(2-naphthalen-1-yl-ethyl)butyramide (6) (770 mg) in trifluoroacetic acid (40ml) was stirred at ambient temperature for 10 minutes. The trifluoroacetic acid was evaporated under reduced pressure and the residue redissolved in diethyl ether (90 ml). Ethereal

- 25 HCl(1M, 10ml) was added and the resulting suspension centrifuged. The diethyl ether was decanted off and more ether(90ml) added to the residue. This mixture was stirred for five minutes and then recentrifuged. The washing/centrifuging procedure was repeated once more and the resulting white solid dried under reduced pressure to give compound (9), (600mg)

- 30 NMR. data in DMSO-d₆ δ 0.6(2d, 6H), 0.95(d, 1H), 1.7(m, 3H), 2.15(m, 1H), 1.9(m, 1H), 3.0 to 3.85(m, 10h), 7.3 to 8.4(m, 7H), 8.9(br.s, 1H), 9.5(br.s, 1H).

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Micro Analysis: %Theory C64.9, H7.7, N6.9
 (1.00 HCl) %Found C64.7, H7.9, N6.8

Starting material (6) was prepared as follows.

- 5 (2S,4S)-2-Formyl-4-BOCsulfanyl-pyrrolidine-1-carboxylic acid allyl ester (1) (1.84 g) in dichloromethane(20ml) was added dropwise over 10 minutes to a mixture of 2-naphthalen-1-ylethylamine (1.0g), sodium triacetoxyborohydride(1.36g) and 4A powdered molecular sieve (3.0 g) in dichloromethane (130ml) cooled to -20°C. and stirred under an argon atmosphere. After the addition was complete the reaction was allowed to warm to
- 10 ambient temperature and stirred for a further 18 hours. The molecular sieves were filtered off and the filtrate stirred with saturated aqueous sodium bicarbonate solution(100 ml) for 5 minutes. The mixture was separated. the organic phase dried over magnesium sulphate and applied to a silica flash column which was then eluted with 1.Ethyl acetate/Hexane(50:50), 2.Ethyl acetate/Hexane(80/20), 3.Ethyl acetate to give (2S,4S)-4-BOCsulfanyl-2[(2-
- 15 naphthalen-1-ylethylamino)-methyl]pyrrolidine-1-carboxylic acid allyl ester (2) (2.2 g) as a colourless gum.

NMR data in CDCl₃, d 1.5(s, 9H), 1.85(m, 1H), 2.5(m, 1H), 2.8(m, 1H), 3.0(m, 3H), 3.2(m, 3H), 3.7(m, 1H), 4.05(m, 2H), 4.55(d, 2H), 5.25(m, 2H), 5.9(m, 1H), 7.43(m, 4H), 7.7(d, 1H), 7.83(m, 1H), 8.05(m, 1H).

20

A mixture of compound (2)(1.2g), isovaleryl chloride(0.61g) and triethylamine(0.77g) in dichloromethane(75ml) was stirred for 1 hour at ambient temperature. The reaction mixture was then applied to a silica flash column which was eluted with ethyl acetate/hexane(20:80) to give compound(3) as a colourless gum (1.3g).

25

Tributyltin hydride(6.46g) was added dropwise over 5 minutes to a stirred mixture of compound(3)(1.23g) and bis(triphenylphosphine)palladium(0) chloride(20 mg) in dichloromethane(75ml). This mixture was stirred at ambient temperature for 30 minutes and then applied to a silica flash column which was eluted with 1.Ethyl acetate/Hexane(50:50), 2.Ethyl acetate, 3.Ethyl acetate/Methanol(95:5). The product

30 obtained was recolumned on an Isolute® C18(10g) column eluting with

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methanol/water(80:20) to give starting material compound (6) as a white solid (769 mg),
m.pt. 86°.

NMR data (CDCl₃) δ 0.9(2d, 6H), 1.3(m, 1H), 1.5(s, 9H), 1.8-2.5(m, 6H), 2.9(m, 1H),
5 3.05-3.9(m, 9H), 7.25-8.35(m, 7H).

Preparation of Compound(10)

A solution of starting material (2S,4S)-2-[(3-methoxypropyl)-(2-naphthalen-1-
10 ylethyl)amino]methyl}-pyrrolidine-4-BOCthiol (compound 7) (78 mg) in trifluoroacetic
acid(5 ml) was stirred at ambient temperature for 30 minutes. The trifluoroacetic acid was
removed under reduced pressure and the residue treated with diethyl ether(5 ml). The ether
was decanted off and the residue dried under reduced pressure for 24 hours to give the
desired end product as a colourless gum (compound10)(70 mg).

15

NMR data (CDCl₃) δ 1.95(m, 4H), 2.05(m, 1H), 3.16-3.62(m, 10H), 3.29(s, 3H), 3.7(m,
1H), 4.15(m, 2H), 7.3-7.65(m, 4H), 7.68(d, 1H), 7.88(d, 1H), 7.98(d, 1H), 11.2(br.s, 2H).

Micro Analysis:	%Theory C48.2, H5.13, N4.32
20 (2.5TFA, 0.25H ₂ O)	%Found C48.5, H5.20, N4.40

Starting material (compound 7) was prepared as follows.

A solution of 4-methoxy-butyraldehyde(140mg) in dichloromethane(10 ml) was added
25 dropwise to a mixture of compound (2)(250 mg), sodium triacetoxyborohydride(338 mg)
and 4A molecular sieves(1.0 g) in dichloromethane(30 ml) stirred under an argon
atmosphere at -20°. After the addition was completed (5 minutes) the reaction mixture was
allowed to warm to ambient temperature and stirred for 18 hours. The molecular sieves
were filtered off and the filtrate washed with saturated sodium bicarbonate solution(20 ml),
30 then brine and dried over magnesium sulphate. The solution was then applied to a silica

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column and eluted with ethyl acetate/hexane(50:50) to give a clear gum. compound(4)(260 mg).

Compound(7) was synthesised from compound(4) analogously to the preparation of
5 compound(6).

NMR data (CDCl₃) δ 1.35(m, 1H), 1.48(s, 9H), 1.74(m, 2H), 2.31(m, 1H), 2.42-3.1(m, 7H), 3.15-3.5(m, 9H), 3.65(m, 1H), 7.28-8.1(m, 7H).

Preparation of Compound(11)

10

Compound(11) was synthesised from starting material (2S,4S)-2-{[(2-(4-methoxyphenyl)methyl)-(2-naphthalen-1-ylethyl)amino]methyl}-pyrrolidine-4-BOCthiol (compound 8) by the method described for the equivalent step in preparation of compound(10).

15

NMR data (CDCl₃) δ 1.9(m, 1H), 2.05(m, 1H), 2.3(m, 1H), 3.1-3.8(m, 8H), 3.82(s, 3H), 4.25(m, 3H), 6.96(d, 2H), 7.42(m, 6H), 7.83(m, 3H).

Micro Analysis: %Theory C55.7, H5.77, N4.06

20 (2TFA, 0.75diethyl ether) %Found C56.0, H5.40, N4.50

The starting material for compound(11) was prepared as follows;

A mixture of compound(2) (200mg), *p*-methoxybenzyl chloride(133 mg), saturated
25 aqueous sodium bicarbonate(5ml) and dichloromethane(20ml) was stirred at ambient temperature for 24 hours. The layers were separated and the organic layer dried, applied to a silica flash column which was then eluted with ethyl acetate/hexane(80:20) to give (2S,4S)-1-allyloxycarbonyl-2-{[(2-(4-methoxyphenyl)methyl)-(2-naphthalen-1-ylethyl)amino]methyl}-pyrrolidine-4-BOCthiol compound(5) as a colourless gum(140
30 mg).

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NMR data (CDCl₃) δ 1.45(s, 9H), 2.0(m, 1H), 2.35(m, 1H), 2.53-4.15(m, 10H), 3.8(s, 3H), 4.6(m, 4H), 5.25(m, 2H), 5.9(m, 1H), 6.85(m, 3H), 7.3(m, 6H), 7.75(m, 2H).

The desired starting material (compound(8)) was synthesised from compound(5) by the
 5 same procedure used to prepare compound(6) from compound (3).

Mass Spec.(ESP+) m/e 507.0

Example 24 (see Scheme 31)

Preparation of

- 10 a) **3-Methyl-N-(naphthalen-1-ylmethyl)-N-([2S,4S]-4-sulfanylpyrrolidin-2-ylmethyl)-butanamide** (compound 23);
- b) **N-(naphthalen-1-ylmethyl)-N-([2S,4S]-4-sulfanylpyrrolidin-2-ylmethyl)-pentanamide** (compound 24);
- c) **N-(naphthalen-1-ylmethyl)-N-([2S,4S]-4-sulfanylpyrrolidin-2-ylmethyl)-2-**
 15 **(pyridin-3-yl)-acetamide** (compound 27);
- d) **3-Methyl-N-(naphthalen-1-ylmethyl)-N-([2S,4S]-4-sulfanylpyrrolidin-2-ylmethyl)-pentanamide** (compound 25);
- e) **3-Methoxy-N-(naphthalen-1-ylmethyl)-N-([2S,4S]-4-sulfanylpyrrolidin-2-ylmethyl)-propanamide** (compound 26) and;
- 20 f) **(2S,4S)-2-([N-(4-methoxybenzyl)-N-(naphthalen-1-ylmethyl)-amino]-methyl)-pyrrolidine-4-thiol** (compound 54).

a) Preparation of Compound 23

A solution of starting material 3-methyl-N-(naphthalen-1-ylmethyl)-N-([2S,4S]-4-
 25 BOCsulfanyl- pyrrolidin-2-ylmethyl)-butanamide (compound(18)) (187mg) in trifluoroacetic acid (10ml) was stirred at ambient temperature for 5 minutes. The trifluoroacetic acid was evaporated under reduced pressure and the resulting residue was redissolved in ethyl acetate (5ml). A solution of hydrogen chloride (2ml/1.0M) was added to the solution followed by diethylether (5ml). The mixture was centrifuged, the solvent
 30 decanted off and the residue was washed with more diethylether (2x15ml) and dried to give the hydrochloride salt of compound(23) as an off-white solid (43mg).

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N.M.R. data (DMSO-d₆) δ 0.83 (m,6H), 0.95(d,1H), 1.68(m,1H), 2.10(m,3H),
2.42(m,1H), 3.10(m,1H), 3.28-3.90(m,5H), 5.20(m,2H), 7.08(d,1H), 7.57(m,3H),
7.87(d,1H), 8.00(m,2H), 9.10-9.80(2br.s,2H)

5

Micro Analysis :	Theory %	C62.7, H7.52, N6.97
(1HCl,0.5H ₂ O)	Found %	C62.4, H7.6, N6.7

The starting material compound(18) was prepared as follows.

10

A solution of (2S,4S)-2-formyl-4-BOCsulfanyl- pyrrolidine-1-carboxylic acid allyl ester (compound (1)) (3.11grm.) in dichloromethane(60 ml.) was added dropwise to a stirred mixture of 1-naphthalenemethylamine (1.71g), 4A molecular sieves(12grms) and sodium triacetoxyborohydride(2.3grms) in dichloromethane (200ml) under an argon
15 atmosphere at -20°. The mixture was stirred for a further 30 minutes at -20°C and then allowed to warm to ambient temperature and stirred for a further 16 hours. The mixture was filtered and washed with aqueous sodium bicarbonate solution (2x200ml), the organic phase further washed with water (200ml), separated, dried over magnesium sulphate and purified by column chromatography, using ethyl acetate/hexane (30:70) as eluent to give
20 (2S,4S)-2-{[naphthalen-1-ylmethyl]-amino)-methyl}-4-BOCsulfanyl- pyrrolidine-1-carboxylic acid allyl ester (compound(12)) as a pale yellow oil (2.09g).

N.M.R. data (CDCl₃) δ 1.50(s,9H), 1.55(m,1H), 1.90(m,1H), 2.50(m,1H), 2.90(m,1H),
3.05(m,1H), 3.20(m,1H), 3.68(m,1H), 4.08(m,2H), 4.23(s,2H), 4.55(d,2H), 5.20(m,2H),
25 5.90(m,1H), 7.47(m,4H), 7.77(m,1H), 7.86(m,1H), 8.13(m,1H).

A mixture of compound(12) (507mg), triethylamine(0.3 ml) and isovaleryl chloride(0.271ml) in dichloromethane (30ml) was stirred at ambient temperature for 1.5 hours and then applied directly to a silica flash column. This was eluted with ethyl
30 acetate/hexane (25:75) and ethylacetate/hexane(35:65) to give 3-Methyl-N-(naphthalen-1-

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ylmethyl)-N-([2S,4S]-1-allyloxycarbonyl-4-BOCsulfanylpyrrolidin-2-ylmethyl)-
butanamide (compound(13)) as a gum (475mg).

N.M.R. data (DMSO-d₆, 373°K) δ 0.90(m,6H), 1.45(s,9H), 1.78(m,1H), 2.18(m,3H),
5 2.50(m,1H), 3.15(q,1H), 3.45(m,1H), 3.70(m,2H), 4.03(q,1H), 4.20(m,1H), 4.45(m,2H),
5.10(m,4H), 5.80(m,1H), 7.20(d,1H), 7.50(m,3H), 7.80(d,1H), 7.92(m,1H), 8.00(m,1H).

Tributyltin hydride(2.22 ml) was added dropwise to a mixture of compound(13) (446 mg),
bis-triphenylphosphine palladium chloride(5.8 mg) in dichloromethane (10ml). The
10 mixture was stirred at ambient temperature under an argon atmosphere for 70 minutes and
then applied directly to a flash column which was eluted with (1)Ethyl acetate/hexane
(50:50) and (2) Ethyl acetate. The product obtained was recolumned on an Isolute® C18
(10g) column, eluting with methanol/water (1) (70:30), (2)(75:25) and (3)(80:20) to give
the desired starting material (compound(18)) as a gum (197mg).

15

N.M.R. data (DMSO-d₆, 373°K) δ 0.90(m,6H), 1.45(m,5H), 1.60(m,1H), 1.68(m,2H),
2.12(m,2H), 2.25(d,2H), 2.40(m,1H), 2.60-3.85(m,8H), 5.14(s,2H), 7.20(d,1H),
7.50(m,3H), 7.83(m,1H), 7.93(m,1H), 8.03(m,1H).

20 b) Preparation of Compound 24

Compound(24) was synthesised by the same procedure used for compound(23) but
substituting appropriate compounds as indicated in Scheme 31.

Compound 24:

N.M.R. data (DMSO-d₆) δ 0.85(m,3H), 1.15-1.75(m,5H), 2.28(t,2H), 3.10(m,1H), 3.33-
25 3.95(m,6H), 5.18(m,2H), 7.20(2d,1H), 7.55(m,3H), 7.85(d,1H), 8.00(m,2H), 8.95-
9.90(2br.s,2H)

Micro Analysis :	%Theory C62.7, H7.52, N6.97
(1HCl .0.5H ₂ O)	%Found C62.5, H7.80, N6.8

30

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Compound(14):

N.M.R. data (CDCl_3) δ 0.90(m.3H), 1.12-2.10(m.6H), 1.48(s.9H), 2.26(m.1H), 2.50(m.1H), 3.00-5.70(m.12H), 5.87(m.1H), 7.07-8.06(m.7H).

5 Compound(19):

N.M.R. data (DMSO-d₆, 373°K) δ 0.84(m,3H), 1.30(m,3H), 1.45(s,9H), 1.55(m,2H), 2.34(m,3H), 2.80(m,2H), 3.45(m,5H), 5.10(m,2H), 7.25(d,1H), 7.50(m,3H), 7.80(d,1H), 7.90(m,1H), 8.03(m,1H).

10 c) Preparation of Compound(27)

Compound(27) was synthesised. in the same manner as the equivalent step for compound(23), from starting material N-(naphthalen-1-ylmethyl)-N-([2*S*,4*S*]-4-BOCsulfanylpyrrolidin-2-ylmethyl)-2-(pyridin-3-yl)-acetamide (compound(22)).

15 Compound(27):

N.M.R. data (DMSO-d₆) δ 1.70(m,1H), 2.50(m,1H), 3.14(m,1H), 3.28-5.10(m,7H), 5.35(m,2H), 7.20-9.00(m,11H), 9.20(br.s,1H), 10.05-10.50(2br.s,1H)

Micro Analysis :	%Theory	C55.10, H6.60, N7.97
(2HCl.2.25H ₂ O. 0.3 diethyl ether)	%Found	C54.80, H6.10, N7.60

20

Starting material (compound(22)) was synthesised as follows.

A mixture of compound(12)(345mg), 4-dimethylamino-pyridine(305mg), 3-pyridylacetic acid hydrochloride(262mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride(348mg) in dichloromethane (30ml) was stirred at ambient temperature.

25 under an argon atmosphere, for 16 hours. The mixture was then purified by silica flash column chromatography, eluting with ethyl acetate/hexane (75:25) and then ethyl acetate to give N-(naphthalen-1-ylmethyl)-N-([2S,4S]-1-allyloxycarbonyl-4-BOCsulfanylpyrrolidin-2-ylmethyl)-2-(pyridin-3-yl)-acetamide (compound (17)) as a colourless gum (394 mg).

30

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Compound(17):

N.M.R. data (DMSO-d₆, 373°K) δ 1.46(s,9H), 1.75(m,1H), 2.50(m,1H), 3.17(q,1H), 3.50(m,1H), 3.75(m,4H), 4.04(m,1H), 4.27(m,1H), 4.45(m,2H), 5.15(m,4H), 5.83(m,1H), 7.25(m,2H), 7.43(t,1H), 7.52(m,2H), 7.58(m,1H), 7.82(d,1H), 7.95(m,2H), 8.40(d,2H).

5

Using the procedure previously described for the equivalent step in synthesis of compound 23, the desired starting material (compound(22)) was synthesised from compound(17).

Compound(22)

10 N.M.R. data (DMSO-d₆, 373°K) δ 1.45(s,9H), 2.38(m,1H), 2.55-4.00(m,10H), 5.20(m,2H), 7.25(m,2H), 7.50(m,4H), 7.90(m,3H), 8.40(m,2H).

d) Preparation of Compound(25)

15 Compound(25) was synthesised using compounds 12, 15 and 20 as intermediates, in the same manner as the equivalent steps for synthesis of compound (27) (see Scheme 31).

Compound(25):

N.M.R. data (DMSO-d₆) δ 0.80(m,6H), 0.95-4.80(m,14H), 5.18(m,2H), 7.08(d,1H),
20 7.55(m,3H), 7.95(m,3H), 8.90-10.15(2br.d,2H).

Micro Analysis : %Theory C59.1, H7.30, N6.27
(2HCl, 0.2H₂O) %Found C59.1, H6.90, N5.9

Compound(15):

25 N.M.R. data (DMSO-d₆, 373°K) δ 0.85(m,6H), 1.15(m,1H), 1.35(m,1H), 1.45(s,9H), 1.75(m,1H), 1.90(m,1H), 2.17(m,1H), 2.30(m,1H), 2.50(m,1H), 3.15(q,1H), 3.45(m,1H), 3.70(m,2H), 4.03(q,1H), 4.20(m,1H), 4.44(d,2H), 5.10(m,4H), 5.80(m,1H), 7.20(d,1H), 7.50(m,3H), 7.80(d,1H), 7.90(m,1H), 8.00(m,1H).

30

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Compound(20):

N.M.R. data (DMSO-d₆, 373°K) δ 0.85(m,6H), 1.25(m,3H), 1.45(s,9H), 1.93(m,1H), 2.27(m,3H), 3.40(m,6H), 5.13(m,2H), 7.25(d,1H), 7.50(m,3H), 7.80(d,1H), 7.90(m,1H), 8.04(m,1H).

5

e) Preparation of Compound(26)

Compound(26) was synthesised using compounds 12, 16 and 21 as intermediates in the same manner as the equivalent steps for synthesis of compound(27) (see Scheme 31).

10 Compound(26):

N.M.R. data (DMSO-d₆) δ 1.70(m,1H), 2.40-4.15(m,14H), 5.20(m,2H), 7.20(2d,1H), 7.55(m,3H), 7.85(m,1H), 8.00(m,2H), 9.05-10.25(2br.d,2H).

Micro Analysis :	%Theory	C59.5, H6.99, N6.93.
(2HCl, 0.2H ₂ O)	%Found	C59.3, H7.30, N6.70

15

Compound(16):

N.M.R. data (DMSO-d₆, 373°K) δ 1.45(s,9H), 1.78(m,1H), 2.40-3.80(m,12H), 4.00(m,1H), 4.20(m,1H), 4.45(m,2H), 5.10(m,4H), 5.80(m,1H), 7.20(d,1H), 7.45(t,1H), 7.50(m,2H), 7.80(d,1H), 7.90(m,1H), 8.00(m,1H).

20

Compound(21):

N.M.R. data (DMSO-d₆, 373°K) δ 1.30(m,1H), 1.48(s,9H), 2.30(m,1H), 2.56-3.70(m,14H), 5.15(m,2H), 7.30(d,1H), 7.47(t,1H), 7.53(m,2H), 7.83(d,1H), 7.94(m,1H), 8.05(m,1H).

25

f) Preparation of Compound(54)

A mixture of starting material (2S,4S)-2-[[N-(4-methoxybenzyl)-N-(naphthalen-1-ylmethyl)-amino]-methyl]-pyrrolidine-4-BOCthiol (compound(53))(100mg) and trifluoroacetic acid(5ml) was stirred at ambient temperature for 1 hour. The trifluoroacetic acid was removed under reduced pressure and the residue coevaporated with diethylether to give compound(54) as a colourless gum (83 mg).

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NMR data (CDCl₃) δ 1.5(m, 1H), 1.75(br.d, 1H), 1.95(m, 1H), 2.6(t, 1H), 3.05(m, 1H), 3.2(d, 1H), 3.35(m, 2H), 3.85(s, 3H), 4.2(s, 2H), 4.6(2d, 2H), 6.95(d, 2H), 7.4(d, 2H), 7.6(m, 4H), 7.9(m, 3H).

5 Micro Analysis: %Theory C52.0. H5.40. N3.90
(2.5TFA. 0.4 diethyl ether) %Found C52.0. H4.92. N3.96.

The starting material was prepared as follows.

A mixture of compound(12)(240 mg), dimethylformamide(20 ml), anhydrous potassium
10 carbonate(80 mg) and *p*-methoxybenzylchloride(0.143ml) was stirred at 70° under an argon atmosphere for 4 hours. The solvent was removed under reduced pressure and the residue purified by column chromatography eluting with ethyl acetate/hexane(20:80) to give a colourless gum (2S,4S)-1-allyloxycarbonyl-2-[{N-(4-methoxybenzyl)-N-(naphthalen-1-ylmethyl)-amino}-methyl]-pyrrolidine-4-BOCthiol (compound(52)) (213 mg).

15 NMR data (CDCl₃) δ 1.45(s, 9H), 2.15(m, 1H), 2.5(m, 1H), 2.8(m, 1H), 3.05(m, 1H), 3.5(m, 2H), 3.8(br.s, 7H), 3.9(m, 1H), 4.2(m, 1H), 4.6(s, 2H), 5.25(m, 2H), 5.9(m, 1H), 6.85(d, 2H), 7.2(d, 2H), 7.4(m, 4H), 7.8(2d, 2H), 8.1(d, 1H).

Tributyltin hydride(0.77ml) was added to a mixture of compound(52) and bis(triphenyl
20 phosphine) palladium (O) chloride(2 mg) in dichloromethane(10 ml). The solution was stirred at ambient temperature for 30 minutes. A second portion of tributyltin hydride(0.335 ml) and bis(triphenylphosphine) palladium (O) chloride(2 mg) were added and the stirring was continued for a further 30 minutes. The mixture was applied directly to a silica flash column which was eluted with ethyl acetate/hexane(25:75),(50:50) and finally ethyl
25 acetate. The product obtained was further purified by reverse phase HPLC on a C18 column eluting with water/methanol/TFA(20:80:0.2) to give the desired starting material (compound(53)) as a colourless gum, (168 mg.)

NMR data (CDCl₃) δ 1.45(s, 9H), 1.55(m, 1H), 2.0(m, 1H), 2.5(m, 1H), 3.1(d, 1H),
30 3.4(m, 3H), 3.6(t, 1H), 3.8(s, 3H), 4.1(2d, 2H), 4.4(d, 1H), 4.6(d, 1H), 6.95(d, 2H), m 7.4(d, 2H), 7.5(m, 4H), 7.9(m, 3H).

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Micro Analysis: %Theory C54.4, H5.40, N3.70
 (2TFA) %Found C55.0, H5.31, N3.89

Example 25 (see Scheme 32)

5 Preparation of

a) (2S,4S)-2[(N-methylnaphthalen-1-ylamino)-methyl]-4-sulfanylpyrrolidine
 (compound 36) and:

b) N-(naphthalen-1-yl)-N-((2S,4S)-4-sulfanylpyrrolidin-2-yl-methyl)-3-methylbutanamide (compound 37).

10

Preparation of Compound 36

A mixture of starting material (2S,4S)-2[(N-methylnaphthalen-1-ylamino)-methyl]-4-BOCsulfanylpyrrolidine (compound (34)) (110 mg) and trifluoroacetic acid (5 ml) was stirred at ambient temperature for 1 hour. The trifluoroacetic acid was removed under
 15 reduced pressure and the residue dried under high vacuum to give compound(36) as a colourless gum(110 mg).

N.M.R. data (CDCl₃) δ 1.7 (m,1H), 1.9 (d,1H), 2.6 (m,1H), 2.95 (s,3H), 3.1 (2d,1H), 3.5 (m,1H), 3.65 (m,3H), 4.05 (m,1H), 7.0 (br. s,1H), 7.4 (t,1H), 7.55 (m,3H), 7.7 (d,1H), 7.85
 20 (m,1H), 8.2 (m,1H).

Micro Analysis: %Found C 45.5, H 4.2, N 5.0
 (2.0TFA, 1.0H₂O) %Theory C 46.3, H 4.67, N 5.4

25 The starting material for compound(36) was prepared as follows;

A mixture of (2S,4S)-2-formyl-4-BOCsulfanyl- pyrrolidine-1-carboxylic acid allyl ester (compound(1)) (711 mg), ethanol(25 ml), 1-naphthylamine(333 mg) and 3A molecular sieves(4.5 g.) was stirred under an argon atmosphere at ambient temperature for 6 hours.
 30 Acetic acid (0.4ml) was added followed by sodium cyanoborohydride(170 mg). The mixture was then stirred for a further 20 hours when the sieves were removed by

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filtration. The filtrate was concentrated under reduced pressure and the residue applied to a silica column and eluted with ethyl acetate/ hexane(20:80) to give (2S,4S)-1-allyloxycarbonyl-2[(naphthalen-1-ylamino)-methyl]-4-BOCsulfanylpyrrolidine (compound(31)) as a clear oil (560 mg).

5

N.M.R. data (CDCl₃) δ 1.5 (s,9H), 1.85 (m,1H), 2.7 (m,1H), 3.35 (m,2H), 3.5 (m,1H), 3.8 (m,1H), 4.2 (m,1H), 4.5 (m,1H), 4.65 (d,2H), 5.3 (2d,2H), 5.95 (m,1H), 6.55 (m,1H), 7.2 (d,1H), 7.3 (t,1H), 7.4 (m,2H), 7.75 (m,1H), 7.9 (m,1H).

- 10 A mixture of (compound(31))(218 mg), dimethylformamide(40ml), iodomethane(0.6 ml.) and anhydrous potassium carbonate(150 mg) was stirred at 80° for 20 hours. The solvent was removed under reduced pressure and the residue taken up in ethyl acetate(30 ml.) and washed with water(20ml). The organic phase was dried over magnesium sulphate, filtered and concentrated under reduced pressure to give (2S,4S)-1-allyloxycarbonyl-2[(N-
- 15 methylnaphthalen-1-ylamino)-methyl]-4-BOCsulfanylpyrrolidine (compound(32)) as a yellow gum (183 mg).

N.M.R. data (CDCl₃) δ 1.45 (s,9H), 2.0 (m,1H), 2.4 (m,1H), 2.85 (s,3H), 3.0 (2d,1H), 3.25 (m,1H), 3.7 (2d,1H), 3.8 (m,1H), 4.1 (m,2H), 4.6 (d,2H), 5.3 (9m,2h), 5.95 (m,1H),

20 7.45 (m,5H), 7.8 (m,1H), 8.25 (m,1H).

To a solution of compound(32)(178 mg) in dichloromethane(10 ml) was added tri-*n*-butyl tin hydride(0.2 ml.) followed by bis(triphenyl phosphine) palladium chloride (2 mg) and the mixture then stirred at ambient temperature. After 10min and 20min a second and

25 third portion of tri-*n*-butyl tin hydride (0.2ml.) and bis(triphenyl phosphine) palladium chloride (2 mg) were added and stirring continued for a further 90 min. The reaction solution was applied direct to a silica column and eluted with ethyl acetate/hexane(25:75), (50:50) and ethyl acetate. The product was further purified on a reverse phase HPLC, C18 column which was eluted with water/methanol/ trifluoroacetic acid(20:80:0.2) to give as a

30 colourless gum the desired starting material (compound(34))(160 mg).

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N.M.R. data (CDCl_3) δ 1.45 (s,9H), 2.2 (s,1H), 2.39 (m,1H), 2.85 (s,3H), 2.9 (2d,1H), 3.1 (2d,1H), 3.25 (m,2H), 3.4 (m,1H), 3.6 (m,1H), 7.15 (d,1H), 7.45 (m,4H), 7.8 (m,1H), 8.35 (m,1H).

5 Micro Analysis: %Found C 50.8, H 5.20, N 4.6
(2.0TFA, 0.5H₂O) %Theory C 49.3, H 5.13, N 4.6

b) Preparation of Compound (37)

10 A mixture of starting material (compound(35))(187 mg) and trifluoroacetic acid(5 ml.) was stirred at ambient temperature for 1 hour. The trifluoroacetic acid was removed under reduced pressure and the residue dried under high vacuum to give a colourless gum, compound (37)(200 mg.).

15 N.M.R. data (CDCl_3) δ 0.8 (m,6H), 1.6-2.2 (m,5H), 2.6 (m,1H), 3.2-5.0 (m,6H), 7.6 (m,5H), 8.0 (m,2H).

Micro Analysis: %Found C 48.4, H 4.80, N 4.5
(2.0 TFA, 1.0H₂O) %Theory C 49.0, H 5.14, N 4.76

20

The starting material was prepared as follows.

Isovaleryl chloride(0.164 ml.) was added dropwise over 10 minutes to a stirred solution of compound(31)(297 mg.), dichloromethane(50 ml) and triethylamine(0.136 ml.). The solution was stirred at ambient temperature for 24 hours. The solvent was removed under
25 reduced pressure and the residue applied directly to a silica column and eluted with ethyl acetate/hexane(25/75) to give a white foam, N-(naphthalen-1-yl)-N-((2S,4S)-1-allyloxycarbonyl-4-BOCsulfanylpyrrolidin-2-yl-methyl)-3-methylbutanamide, (compound(33))(329 mg).

N.M.R. data (CDCl_3) δ 0.75 (m,6H), 1.5 (s,9H), 1.65 -2.7 (m,5H), 3.15 -6.0 (m,9H),
30 7.25 (m,1H), 7.5 (m,3H), 7.7 (m,1H), 7.9 (m,2H).

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- To a solution of compound(33)(296 mg.) in dichloromethane(10 ml) was added tri-n-butyl tin hydride (0.3 ml.) followed by bis(triphenyl phosphine) palladium chloride(2 mg.). The solution was stirred at ambient temperature. After 10min and 20min a second and third portion of tri-n-butyl tin hydride(0.3 ml.) and bis(triphenyl phosphine) palladium chloride(2 mg) were added and the stirring continued for a further 30 minutes. The reaction solution was applied directly to a silica column which was then eluted with ethyl acetate/hexane(25:75), (50:50) and ethyl acetate. The product was further purified on a reverse phase HPLC . C18 column eluting with water/methanol/trifluoroacetic acid(20:80:0.2) to give the desired starting material. (compound (35))(216 mg.).
- 10 N.M.R. data (CDCl_3) δ 0.8 (m,6H), 1.49 (s,9H), 1.1 -2.2 (m,6H), 2.9 -5.6 (m,6H), 7.4 - 8.0 (m,7H).

Micro Analysis:	%Found	C 57.0, H 6.20, N 4.80
(1.0TFA, 0.75H ₂ O)	%Theory	C 56.9, H 6.45; N 4.91

15 Example 26 (see Scheme 33)

Preparation of

- a) **3-Methyl-N-(3,3-diphenylpropyl)-N-([2S,4S]-4-sulfanylpyrrolidin-2-ylmethyl)-butanamide** (compound 43) and;
- b) **N-(3,3-diphenylpropyl)-N-([2S,4S]-4-sulfanylpyrrolidin-2-ylmethyl)-butanamide** (compound 44)
- 20

Compounds (43) and (44) were synthesised using the procedure described in Example 23 using appropriate starting materials and intermediates as set out in Scheme 33.

25 a) Preparation of Compound (43)

Compound (43) :

NMR data (DMSOd6 at 373 ° K.) δ 0.9(d, 6H), 1.7(m, 1H), 2.1(m, 1H), 2.33(m, 2H), 2.45(m, 1H), 2.9-4.00(m, 9H), 4.2-4.95(m, 2H), 7.3-8.1(m, 10H), 9.65(v.br.s, 2H)

Micro Analysis: %Theory C64.8, H7.7, N5.9

30 1.00HCl. 1H₂O %Found C64.5, H7.9, N6.0

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The starting material 3-Methyl-N-(3,3-diphenylpropyl)-N-([2S,4S]-4-BOCsulfanylpiperidin-2-ylmethyl)-butanamide (compound 41) was synthesised from compound (1) and 3,3-diphenylpropylamine using a similar procedure to that outlined in Example 23.

5

Compound (38) :

NMR data (CDCl₃) δ 1.5(s, 9H), 1.8(m, 1H), 2.19(m, 2H), 2.42(m, 1H), 2.55(m, 2H), 2.7(m, 1H), 2.82(m, 1H), 3.19(m, 1H), 3.67(m, 1H), 4.0(m, 3H), 4.55(d, 2H), 5.2(2d, 2H), 5.9(m, 1H), 7.2(m, 10H).

10

Compound (39) :

NMR data (CDCl₃) δ 0.75-1.0(m, 6H), 1.22(m, 1H), 1.5(s, 9H), 1.78-2.02(m, 2H), 2.3(m, 4H), 3.2(m, 3H), 3.4-4.2(m, 6H), 4.52(m, 2H), 5.21(m, 2H), 5.9(m, 1H), 7.2(m, 10H) .

15 Compound (41) :

NMR data (CDCl₃) δ 0.75-1.00(m, 6H), 1.25(m, 1H), 1.5(s, 9H), 1.85-2.4(m, 6H), 2.83(m, 1H), 3.05-3.47(m, 6H), 3.6(m, 1H), 3.87(2t, 1H), 7.25(m, 10H) .

b) Preparation of Compound (44)

20 Characterisation data is set out below:

Compound (44):

NMR data (DMSO-d₆ at 373° K) δ 1.65(m, 1H), 1.85(s, 3H), 2.32(q, 2H), 2.45(m, 1H), 2.69-4.3(m, 9H), 7.2(m, 10H), 9.37(v.br.s, 2H).

Micro Analysis: %Theory C 63.3, H 7.3, N, 6.6

25 1.00 HCl, 0.75H₂O %Found C63.1, H 7.3, N, 6.7

Compound (40):

NMR data (CDCl₃) δ 1.5(s, 9H), 1.82(s, 3H), 1.6-2.5(m, 4H), 3.2(m, 3H), 3.32-4.25(m, 6H), 4.54(m, 2H), 5.23(m, 2H), 5.9(m, 1H), 7.23(m, 10H).

30

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Compound (42):

NMR data (CDCl₃) δ 1.48(s, 9H), 1.8(m, 1H), 1.87(s, 2H), 2.07(s, 1H), 2.33(m, 3H), 2.83(m, 1H), 3.28(m, 6H), 3.6(m, 1H), 3.85(m, 1H), 7.25(m, 10H).

5 Example 27 (see Scheme 34)

Preparation of

a) **3-Methyl-N-(naphthalen-2-ylmethyl)-N-([2S,4S]-4-sulfanylpyrrolidin-2-ylmethyl)-butanamide** (compound 50) and;

b) **N-(naphthalen-2-ylmethyl)-N-([2S,4S]-4-sulfanylpyrrolidin-2-ylmethyl)-acetamide** (compound 51)

10

Compounds (50) and (51) were synthesised using the procedure described in Example 23 using appropriate starting materials and intermediates as set out in Scheme 34.

15 a) Preparation of Compound (50).

Compound 50:

NMR data (DMSO-d₆) δ 0.75-1.1(m, 6H), 1.63(m, 1H), 2.1(m, 1H), 2.48(m, 1H), 2.83(m, 3H), 3.0-4.95(m, 8H), 7.17(m, 7H).

Micro Analysis: %Theory C64.2, H7.44, N7.13.

20 (1.0 HCl) %Found C64.0, H7.40, N7.10.

Starting material 3-Methyl-N-(naphthalen-2-ylmethyl)-N-([2S,4S]-4-BOCsulfanylpyrrolidin-2-ylmethyl)-butanamide (compound (48)) was synthesised from compound (1) and 2-naphthylmethylamine.

25

Compound (45):

NMR data (CDCl₃) δ 1.48(s, 9H), 1.92(m, 1H), 2.5(m, 1H), 2.82(m, 1H), 2.96(m, 1H), 3.2(2d, 1H), 3.7(m, 1H), 3.96(s, 2H), 4.08(m, 2H), 4.54(m, 2H), 5.2(m, 2H), 5.9(m, 1H), 7.42(m, 3h), 7.8(m, 4H).

30

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Compound (46):

NMR data (CDCl₃) δ 0.96(2d, 6H), 1.48(s, 9H), 1.9(m, 1H), 2.13-2.6(m, 4H), 3.3(m, 1H), 3.72(m, 2H), 4.15(m, 2H), 4.5(m, 2H), 4.76(m, 1H), 5.2(m, 2H), 5.9(m, 1H), 7.48(m, 3H), 7.73(m, 4H).

5

Compound (48):

NMR data (CDCl₃) δ 0.98(2d, 6H), 1.3(m, 1H), 1.48(s, 9H), 2.3(m, 4H), 2.9(m, 1H), 3.1-3.7(m, 5H), 4.85(m, 2H), 7.15-7.9(m, 7H).

10 b) Preparation of Compound (51)

Characterisation data is set out below.

Compound 51:

NMR data (DMSO-d₆ at 373 °K) δ 1.7(m, 1H), 2.14(s, 3H), 2.47(m, 1H), 2.8-4.00(m, 6H), 4.8(m, 2H), 7.32-8.1(m, 7H).

15

Micro Analysis:	%Theory C64.2, H7.44, N7.13.
(1.00 HCl)	%Found C64.0, H7.40, N7.10.

Compound (47):

20 NMR data (CDCl₃) δ 1.5(s, 9H), 1.9(m, 1H), 2.12(s, 2H), 2.29(s, 1H), 2.5(m, 1H), 3.18-3.5(m, 10H), 5.2(m, 2H), 5.95(m, 1H), 7.2-7.89(m, 7H).

Compound (49):

NMR data (CDCl₃) δ 1.3(m, 1H), 1.47(s, 9H), 2.15(s, 2H), 2.3(s, 1H), 2.35(m, 1H), 2.88(m, 1H), 3.1-3.7(m, 5H), 4.85(m, 2H), 7.4-7.9(m, 7H).

25

Example 28 (see scheme 35)

(2S)-2-({4-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-naphthalene-2-carbonyl)-amino)-4-methylsulfanylbutyric acid methyl ester (compound 30)

30 Starting material (2S)-2-({4-[(2S,4S)-4-BOCsulfanylpyrrolidin-2-ylmethyl]-amino}-naphthalene-2-carbonyl)-amino)-4-methylsulfanylbutyric acid methyl ester **30e**

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(72.1mg,0.132mmol) was deprotected (analogously as for the equivalent step in **Example 15**) to give the title compound **30**.76mg (97.8%).

¹H NMR (CDCl₃+CD₃COOD,200MHz) δ 1.75-2.0(1H,m); 2.0-2.5(5H+DMSO,m); 2.55-3.0(3H,m); 3.15-3.4(1H,m); 3.5-3.7(1H,m); 3.7-3.9(6H,m); 4.2-4.4(1H,m);

5 4.9-5.05(1H,m); 7.0-8.1(6H,m,ArH).

MS (ESP⁺) m/z 448 (M+H)⁺.

Anal.Calcd for C₂₂ H₂₉ N₃ S₂ O₃ 1.25 TFA C,49.9;H,5.17;N,7.12

Found

C,49.6;H,5.3;N,6.7

10 Starting material **30e** was prepared as follows.

Compound 30a

2-Napthoic acid was nitrated with conc HNO₃ (Tetrahedron 49,17.3655.1993) to give a mixture of nitro-acids **30a**.containing the required 4-Nitro-2-Napthoic acid.

MS (ESP⁺) m/z 216 (M-H)⁺.

15

Compound 30b

Oxalyl chloride (6.0mL,68.7mmol) was added dropwise to a stirred solution of the nitro acid mixture,**30a**(7.3g,33.6mmol) in a mixture of DMF(1.0mL) and CH₂Cl₂ (100mL) at 0°C under argon.The solution was allowed to warm to RT stirred 18hrs. evaporated to

20 dryness and azeotroped with toluene(2x25mL).The resulting residues were redissolved in CH₂Cl₂ (100mL) and cooled to 0°C under argon.

Et₃N (7.0mL,50mmol) was then added, followed by L-Methionine methylester hydrochloride (7.4g,37mmol), portionwise, such that the internal temperature did not rise above 10°C.The reaction mixture was left to warm to room temperature and stirred for 18hr

25 washed with water(100mL) ,dried over MgSO₄ ,filtered and concentrated to a viscous brown gum.This was then purified by flash chromatography on SiO₂(Merck 9385).eluting with 25%EtOAc/i-Hexane.Appropriate fractions were combined and evaporated to give **30b** as a viscous orange gum,490mg(4%).

¹H NMR (CDCl₃,200MHz) δ 2.1-2.5(5H,m); 2.55-2.75(2H,m); 3.85(3H,s);

30 4.9-5.1(1H,m);7.32(1H,d); 7.6-8.0(2H,m); 8.05(1H,dd); 8.5-8.7(3H,m).

MS (ESP⁺) m/z 363 (M+H)⁺.

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Compound 30c

30b (450mg, 1.24mmol) was reduced (analogously as for the equivalent step in **Example 22**) to give the corresponding aniline **30c** as a yellow gum. 310mg (75.3%)

¹H NMR (CDCl₃, 250MHz) δ 2.0-2.45(5H, m); 2.5-2.75(2H, m); 3.83(3H, s);

5 4.3(2H, bs, NH₂); 4.9-5.05(1H, m); 7.0(1H, d, NHCO); 7.2(1H, d); 7.45-7.65(2H, m); 7.72(1H, s); 7.8-8.0(2H, m).

MS (ESP⁺) m/z 333 (M+H)⁺, 271, 170.

Compound 30d

10 **30c** (300mg, 0.9mmol) was coupled with the aldehyde **22b** (428mg, 1.36mmol) under the conditions employed to synthesise **22g** using MeOH as solvent and in the presence of 3A^o molecular sieves as drying agent to give **30d** as yellow gum. 460mg (76.5%)

MS (ESP⁺) m/z 632 (M+H)⁺

15 Compound 30e

30d (450mg, 0.7mmol) was deprotected (analogously as for the equivalent step in **Example 15**) to give the desired starting material **30e**. 220mg (56.4%)

¹H NMR (CDCl₃, 200MHz) δ 1.4-1.9(10H+H₂O, m); 2.0-2.75(9H, m); 2.95(1H, q);

3.1-3.35(1H, m); 3.35-3.55(2H, m); 3.55-3.8(2H, m); 3.82(3H, s, CO₂Me); 4.98(1H, m);

20 5.15(1H, bs, NH); 6.9-7.1(2H, m, ArH+NHCO); 7.4-7.6(2H, m); 7.61(1H, d); 7.8-8.0(2H, m).

MS (ESP⁺) m/z 548 (M+H)⁺, 448.

Example 29 (see scheme 36)

25 Preparation of

a) (2S)-2-({3-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-naphthalene-1-carbonyl)-amino)-4-methylsulfanylbutyric acid methyl ester (compound 31)

b) (2S)-2-({3-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-naphthalene-1-carbonyl)-amino)-4-methylsulfanylbutyric acid (compound 31f)

30

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a) Preparation of Compound 31

31e (55mg, 0.1mmol) was deprotected (analogously as for the equivalent step in **Example 15**) then treated with Et₂O.HCl to give the title compound, **31** as a white solid.

(37mg, 64.8%)

5 ¹H NMR (DMSO-D₆+CD₃CO₂D, 250MHz) δ 1.05(1H, t, (CH₂CH₂)₂O); 1.6-1.8(1H, m); 1.9-2.15(4H, m); 2.3-2.7(4H+DMSO, m); 3.0-4.0(9H+(CH₃CH₂)₂O); 4.55-4.7(1H, m); 6.95(1H, s); 7.1(1H, s); 7.15(1H, t); 7.32(1H, t); 7.62(1H, d); 7.92(1H, d)

MS (ESP⁺) m/z 448 (M+H)⁺.

Anal. Calcd for C₂₂H₂₉N₃S₂O₃ 2.7HCl 0.3Et₂O. C, 49.0; H, 6.15; N, 7.39

10 Found

C, 49.1; H, 6.1; N, 7.2

Compound 31a

3-Nitro-1-naphthoic acid **31a** was synthesised from 3-nitro-1,8-naphthalic anhydride according to the method of G.J. Leuck et al (Journal of the American Chemical Society

15 51, 1831, 1929).

Compound 31b

3-Nitro-1-Naphthoic acid **31a** (5.0g, 23.04mmol) was coupled with L-Methionine methylester hydrochloride (analogously as for the equivalent step in **Example 22**) to give

20 **31b** as a white crystalline solid, 2.53g (30.3%)

¹H NMR (CDCl₃, 200MHz) δ 2.0-2.5(5H, m); 2.55-2.75(2H, m); 3.85(3H, s); 5.05(1H, m); 6.9(1H, d, NH); 7.6-7.85(2H, m); 8.0-8.15(1H, m); 8.3-8.5(2H, m); 8.83(1H, m)

MS (ESP⁺) m/z 363 (M+H)⁺

25 Compound 31c

31b (2.3g, 6.35mmol) was reduced (analogously as for the equivalent step in **Example 22**) to give the corresponding aniline **31c** as a yellow gum, 1.75g (83%)

¹H NMR (CDCl₃, 250MHz) δ 2.05-2.2(4H, m); 2.25-2.45(1H, m); 2.63(2H, m); 3.83(3H, s); 5.03(1H, m); 6.66(1H, d); 7.05(1H, m); 7.15(1H, m); 7.28(1H, m); 7.39(1H, m);

30 7.6(1H, m); 8.15(1H, m)

MS (ESP⁺) m/z 333 (M+H)⁺, 170.

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Compound 31d

31c(1.7g,5.12mmol) was coupled with the aldehyde **22b**(1.76g,5.59mmol), (analogously as for the equivalent step in **Example 30**) to give **31d** as an off-white foam.2.95g(91.3%).

¹H NMR (CDCl₃+CD₃COOD,250MHz) δ1.5(9H,s),1.9(1H,m);

5 2.0-2.25(4H+CH₃COOH,m);2.25-2.44(1H,m);2.55-2.75(3H,m);3.25-3.53(2H,m);

3.55-3.7(1H,m);3.7-3.95(4H,m);4.1-4.25(1H,m);4.25-4.4(1H,m);4.55-4.8(2H,m);

5.03(1H,m);5.15-5.45(2H,m);5.96(1H,m);6.9-7.5(4H+CHCl₃,m);7.66(1H,m);

8.1(1H,m)

MS (ESP+) m/z 632 (M+H)⁺.

10

Compound 31e

31d (2.0g,3.17mmol) was deprotected (analogously as for the equivalent step in **Example15**) to give the desired starting material **31e** as a pale yellow foam.1.62g(93.4%).

¹H NMR (CDCl₃,300MHz) δ2.4-2.6(10H,m);1.85(4H,bs);2.0-2.2(4H,m);

15 2.35(1H,m);2.5(1H,m);2.65(2H,t);2.9(1H,m);3.1(1H,m);3.3(1H,m);3.4(1H,m);

3.55(1H,m);3.65(1H,m);3.8(3H,s);5.02(1H,m);6.65(1H,d);6.9(1H,m);7.1(1H,m);

7.2-7.3(1H+CHCl₃,m);7.4(1H,m);7.62(1H,m);8.1(1H,m)

MS (ESP+) m/z 548 (M+H)⁺,448.

20 b) Compound 31f

31e(180mg,0.33mmol) was hydrolysed (analogously as for **Example 16**) then purified by reverse phase HPLC (Dynamax® 60A,C₁₈,8m prep column), eluting with 50%MeOH/H₂O (0.1% TFA) to give product **31f** as a white foam,126mg(65.9%).

¹H NMR (DMSO-D₆+CD₃COOD,300MHz) δ1.5-1.8(1H,m);1.9-2.1(5H,m);

25 2.4-2.7(3H+DMSO,m);3.0-3.1(1H,m);3.4-3.7(4H,m);3.75-3.9(1H,m);4.57(1H,m);

6.9(1H,m);7.07(1H,m);7.17(1H,m);7.35(1H,m);7.63(1H,m);7.95(1H,m)

MS (ESP+) m/z 434 (M+H)⁺,285.

Anal.Calcd for C₂₁H₂₇N₃S₂O₃.1.3TFA C,48.7;H,4.9;N,7.22

Found C,48.6;H,4.9;N,7.1

30

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Example 30 (see Scheme 37)

Preparation of

a) (2S)-2-((-3-phenyl-5-((2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl)-amino)-phenylcarbonyl)-amino)-4-methylsulfanylbutyric acid methyl ester (compound 32)

5 and;

b) (2S)-2-((-3-phenyl-5-((2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl)-amino)-phenylcarbonyl)-amino)-4-methylsulfanylbutyric acid (compound 32f)

a) Preparation of Compound 32

10 Starting material compound 32e (55mg,0.096mmol) was deprotected (analogously as for the equivalent step in **Example 15**) to give the title compound **32** as a white foam (56mg).

¹H NMR (CDCl₃,250MHz) δ1.6-1.85(1H,m);1.9-2.4(6H+CH₃C₅H₆);2.45-2.7(3H,m);
3.1-3.25(1H,m);3.35-4.1(1H+H₂O,m);4.75-4.95(1H,m);6.8(1H,m);6.9-7.05(1H,m);
7.1-7.55(6H+CH₃C₆H₅+CHCl₃,m,)

15 MS (ESP+) m/z 474 (M+H)⁺.

Anal.Calcd for C₂₄H₃₁N₃O₃S₂.2TFA.0.75toluene C,51.8;H,5.1;N,5.45

Found C,51.6;H,5.2;N,5.1

Starting material 32e was prepared as follows.

20

Compound 32a

Saturated NaHCO₃(aq) (90mL) was added to a stirred solution of methyl-3-bromo-5-nitrobenzoate (4.0g,15.38mmol) (Mindl and Vecera, Coll.Czech.Chem.Comm. **38**,3496,1973.) and phenyl boronic acid (2.0g,16.38mmol) in dimethoxyethane (180mL).

25 Tetrakis(triphenylphosphine)palladium(0), (444mg,0.38mmol) was added and the mixture heated at reflux for 1hr. The resulting black solution was allowed to cool to RT then quenched with saturated NaHCO₃(aq)(400mL). The aqueous was extracted with EtOAc(200mL),then acidified to pH3 with 2N HCl. The resulting suspension was filtered,washed with water and azeotroped with toluene (3x25mL) to give **32a** as an off-
30 white solid which was triturated with i-Hexane.filtered and dried.2.6g(69.5%).

¹H NMR (DMSO-D₆,300MHz) δ7.5(3H,m);7.8(2H,m);8.4-8.7(3H,m)

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MS (ESP⁺) m/z 242 (M-H)⁺.Anal. Calcd for C₁₃H₉NO₄ : C.64.2:H.3.73:N.5.76

Found C.64.0:H.3.7:N.5.6

5 Compound 32b

32a (3.1g, 12.76mmol) was coupled with L-Methionine methylester hydrochloride (analogously as for the equivalent step in **Example 22**) to give **32b**. 4.9g (99%).

¹H NMR (CDCl₃, 200MHz) δ 2.1-2.45 (5H, m); 2.65 (2H, t); 3.83 (3H, s); 4.99 (1H, m); 7.2-7.35 (1H + CHCl₃, m); 7.4-7.6 (3H, m); 7.6-7.7 (2H, m); 8.38 (1H, m); 8.58 (2H, m)

10 MS (ESP⁺) m/z 389 (M+H)⁺.Anal. Calcd for C₁₉H₂₀N₂O₅S C.58.8:H.5.19:N.7.21

Found C.58.8:H.5.1:N.7.2

Compound 32c

15 **32b** (3.0g, 7.73mmol) was reduced (analogously as for the equivalent step in **Example 30**) to give the corresponding aniline **32c**. 2.43g (87.8%).

¹H NMR (CDCl₃, 250MHz) δ 2.0-2.2 (4H, m); 2.2-2.4 (1H, m); 2.6 (2H, m); 3.8 (3H, s); 3.9 (2H, bs, NH₂); 4.93 (1H, m); 6.93 (1H, d, NHCO); 7.03 (1H, m); 7.12 (1H, m); 7.3-7.5 (4H, m); 7.5-7.65 (2H, m)

20 MS (ESP⁺) m/z 359 (M+H)⁺.Compound 32d

32c (1.0g, 2.8mmol) was coupled with the aldehyde **22b** (880mg, 2.8mmol) (analogously as for the equivalent step in **Example 30**) to give **32d**. 1.51g (82.3%)

25 ¹H NMR (CDCl₃ + CD₃COOD, 250MHz) δ 1.5 (9H, s); 1.8-2.0 (1H, m); 2.0-2.4 (5H + CH₃COOH, m); 2.5-2.75 (3H, m); 3.2-3.45 (2H, m); 3.5-3.7 (1H, m); 3.7-3.9 (4H, m); 4.0-4.4 (2H, m); 4.5-4.75 (2H, m); 4.9-5.05 (1H, m); 5.1-5.45 (2H, m); 5.8-6.1 (1H, m); 7.03 (1H, m); 7.1-7.5 (5H + CHCl₃, m); 7.55-7.7 (2H, m)

MS (ESP⁺) m/z 658 (M+H)⁺.30 Anal. Calcd for C₃₃H₄₃N₃O₇S₂ · 0.1H₂O C.59.9:H.6.61:N.6.35

Found C.59.7:H.6.8:N.6.2

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Compound 32e

32d (1.1g, 1.67mmol) was deprotected (analogously as for the equivalent step in **Example 15**) to give the desired starting material **32e**. 800mg (83.4%).

¹H NMR (CDCl₃, 250MHz) δ 1.25 (1.5H, t, CH₃CH₂COCH₃); 1.4-1.6 (10H, m);

5 1.9 (2H, bs, NH+H₂O); 2.0-2.22 (4H+CH₃CH₂CO₂CH₃); 2.23-2.55 (2H, m);

2.51-2.65 (2H, m); 2.9 (1H, m); 3.12 (1H, m); 3.2-3.75 (4H, m); 3.8 (3H, m);

4.13 (1.3H, q, CH₃CH₂CO₂CH₃); 4.45 (1H, bs, NH); 4.95 (1H, m);

6.85-7.0 (2H, m, ArH+NHCO); 7.07 (1H, m); 7.2-7.5 (4H+CHCl₃, m); 7.5-7.65 (2H, m)

MS (ESP+) m/z 574 (M+H)⁺, 474.

10 Anal. Calcd for C₂₉H₃₉N₃O₅S₂·0.5EtOAc C, 60.3; H, 7.02; N, 6.8

Found C, 59.9; H, 7.1; N, 6.6

b) Preparation of Compound 32f

15 Starting material **32e** (140mg, 0.244mmol) was hydrolysed (analogously as for the equivalent step in **Example 31**) to give the desired product **32f** as a white foam, 96.3mg (64.9%).

¹H NMR (DMSO-D₆+CD₃COOD, 250MHz) δ 1.5-1.8 (1H, m); 1.9-2.2 (5H, m);

3.05 (1H, q); 3.15-3.6 (7H, m); 3.65-3.9 (1H, m); 4.45-4.65 (1H, m); 6.95-7.05 (1H, m);

20 7.05-7.2 (1H, m); 7.25-7.5 (4H, m); 7.55-7.7 (2H, m).

MS (ESP+) m/z 460 (M+H)⁺, 279.

Anal. Calcd for C₂₃H₂₉N₃S₂O₃·1.3TFA C, 50.6; H, 5.02; N, 6.91

Found C, 50.6; H, 5.1; N, 7.2

25 The starting material was prepared as described in a) immediately above.

Example 31 (see Scheme 38)

Preparation of

a) (2S)-2-({2-phenyl-5-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-

30 phenylcarbonyl)-amino)-4-methylsulfanylbutyric acid methyl ester (compound 33)

and;

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b) (2S)-2-((2-phenyl-5-((2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl)-amino)-phenylcarbonyl)-amino-4-methylsulfanylbutyric acid (compound 33f)

a) Preparation of Compound 33

- 5 Starting material **33e** (53.4mg, 0.093mmol) was deprotected (analogously as for the equivalent step in **Example 31**) to give the title compound **33** as a white solid, 43.2mg (87%).

¹H NMR (DMSO-D₆+CD₃COOD, 300MHz) δ 1.5-1.9 (3H+CH₃COOH, m); 1.95 (3H, s); 2.0-2.3 (2H, m); 2.4-2.65 (1H+DMSO, m); 3.0-3.15 (1H, m); 3.3-3.9 (8H, m);

- 10 4.25-4.4 (1H, m); 6.7 (1H, m); 6.78 (1H, m); 7.1-7.4 (6H, m).

MS (CI⁺) m/z 474 (M+H)⁺.

Anal. Calcd for C₂₄H₃₁N₃S₂O₃·1.75TFA C, 53.6; H, 6.14; N, 7.82

Found C, 53.6; H, 6.3; N, 7.7

- 15 The starting material was prepared as follows.

Compound 33a

2-Bromo-5-nitrobenzoic acid (12.28g, 0.05mmol) was coupled with benzene boronic acid (6.7g, 0.055mmol), (analogously as for the equivalent step in **Example 32**) to give **33a** as a white solid, 10.95g (90.3%).

- 20 ¹H NMR (DMSO-D₆, 300MHz) δ 7.3-7.5 (5H, m); 7.65 (1H, m); 8.35 (1H, m); 8.45 (1H, m).
MS (ESP-) m/z 242 (M-H)⁻, 198.

Compound 33b

33a (3.58g, 14.7mmol) was coupled with L-Methionine methyl ester hydrochloride

- 25 (3.25, 16.2mmol), (analogously as for the equivalent step in **Example 32**) to give **33b** as a pale yellow solid, 3.02g (52.6%)

¹H NMR (CDCl₃, 300MHz) δ 1.7-2.2 (7H, m); 3.7 (3H, s); 4.7 (1H, m); 6.05 (1H, m, NH); 7.35-7.6 (6H, m); 8.33 (1H, m); 8.55 (1H, m)

MS (ESP+) m/z 389 (M+H)⁺.

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Compound 33c

33b (1.0g, 2.6mmol) was reduced (analogously as for the equivalent step in **Example 30**) to give the corresponding aniline **33c**. 725mg (78.6%).

¹H NMR (CDCl₃, 300MHz) δ 1.6-1.8 (1H, m); 1.8-2.15 (6H, m); 3.6 (3H, s);

5 3.7-3.9 (2H, bs, NH₂); 4.6-4.7 (1H, m); 5.85 (1H, d, NHCO); 6.79 (1H, m); 7.0 (1H, m); 7.15 (1H, d); 7.2-7.45 (5H + CHCl₃, m).

MS (ESP+) m/z 359, (M+H)⁺, 196.

Compound 33d

10 **33c** (710mg, 1.98mmol) was coupled with the aldehyde **22b** (625mg, 1.98mmol) (analogously as for the equivalent step in **Example 30**) to give **33d**. 1.1g (84.4%).

¹H NMR (CDCl₃ + CD₃COOD, 250MHz) δ 1.5 (9H, s); 1.6-2.2 (8H + CH₃COOH, m); 2.5-2.75 (1H, m); 3.2-3.4 (2H, m); 3.45-3.9 (5H, m); 4.05-4.35 (2H, m); 4.5-4.8 (3H, m); 5.15-5.45 (2H, m); 5.8-6.1 (1H, m); 6.75-6.9 (1H, m); 6.9-7.05 (1H, m); 7.1-7.23 (1H, m);

15 7.25-7.45 (5H + CHCl₃, m).

MS (ESP+) m/z 658 (M+H)⁺.

Anal. Calcd for C₃₃H₄₃N₃S₂O₇ C, 60.3; H, 6.59; N, 6.39

Found C, 60.0; H, 6.9; N, 6.2

20 Compound 33e

33d (1.0g, 1.52mmol) was deprotected (analogously as for the equivalent step in **example 15**) to give the desired starting material **33e**. 658mg (75.4%).

¹H NMR (CDCl₃ + CD₃COOD, 250MHz) δ 1.5 (9H, s); 1.6-2.2 (8H + CH₃COOH, m);

2.55-2.75 (1H, m); 3.25-3.4 (1H, m); 3.5-3.75 (5H, m); 3.75-4.2 (3H, m);

25 4.55-4.75 (1H, m); 6.7-6.85 (1H, m); 6.85-6.97 (1H, m); 7.1-7.25 (1H, m);

7.25-7.48 (5H + CHCl₃, m).

MS (ESP+) m/z 574 (M+H)⁺, 474.

Anal. Calcd for C₂₉H₃₉N₃O₅S₂ C, 60.7; H, 6.85; N, 7.32

Found C, 60.7; H, 7.20; N, 7.30

30

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b) Preparation of Compound 33f

Starting material **33e** (100mg, 0.174mmol) was hydrolysed (analogously as for the equivalent step in **Example 31**) to give **33f** as a white foam, 64.6mg (59.8%).

¹H NMR (DMSO-D₆+CD₃COOD, 300MHz) δ 1.5-2.0 (6H, CH₃COOH, m);

5 2.0-2.3 (2H, m); 2.3-2.7 (1H, DMSO); 3.0-3.1 (1H, m); 3.2-3.9 (5H, m); 4.2-4.35 (1H, m); 6.6-6.9 (2H, m); 7.1-7.4 (6H, m).

MS (ESP+) m/z 460 (M+H)⁺, 311.

Anal Calcd for C₂₃H₂₉N₃O₃S₂·1.4TFA C, 50.0; H, 4.95; N, 6.79

Found C, 49.9; H, 5.1; N, 6.7

10

Starting material **33e** was prepared as described in a) immediately above.

Example 32 (see Scheme 39)

Preparation of

- 15 a) (2S)-2-{2-Benzyl-5-[(4-sulfanylpyrrolidin-2-ylmethyl)-amino]-benzoylamino}-4-methylsulfanylbutyric acid methyl ester (compound 34) and;
 b) (2S)-2-{2-Benzyl-5-[(4-sulfanylpyrrolidin-2-ylmethyl)-amino]-benzoylamino}-4-methylsulfanylbutyric acid (compound 34h)

20 a) Preparation of Compound 34

Starting material **34g** (500mg, 0.85mmol) was deprotected (analogously as for the equivalent step in **Example 31**) to give the title compound **34** as a white solid, 454mg (89.3%).

¹H NMR (DMSO-D₆+CD₃COOD, 300MHz) δ 1.5-1.7 (1H, m); 1.85-2.1 (5H, m);

25 2.35-2.6 (3H+DMSO, m); 2.9-3.1 (1H, m); 3.1-3.8 (8H, m); 3.9 (2H, q); 4.4-4.6 (1H, m); 6.5-6.7 (>1H, m); 6.9-7.0 (1H, m); 7.0-7.3 (6H, m).

MS (ESP+) m/z 488 (M+H)⁺, 325.

Anal. Calcd for C₂₅H₃₃N₃S₂O₃·3HCl C, 50.3; H, 6.08; N, 7.04

Found C, 50.4; H, 6.3; N, 7.3

30 Starting material **34g** was prepared as follows.

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Compound 34a

A solution of 2-bromo-5-nitrobenzoic acid (9.0g,36.6mmol) in MeOH (200mL) was treated with SO_2Cl_2 (2.0mL) and the resulting solution heated at reflux for 18hrs. The reaction mixture was then evaporated, pre-absorbed on SiO_2 (Merck.9385) and

- 5 chromatographed, eluting with 10%EtOAc/i-Hexane. Appropriate fractions were combined and evaporated to give **34a** as a crystalline white solid, 8.38g(88.1%)
 ^1H NMR (CDCl_3 ,300MHz) δ 4.0(3H,s, CO_2CH_3);7.85(1H,m);8.18(1H,m);8.63(1H,m).

Compound 34b

- 10 A solution of benzyl bromide (2.0mL,17.3mmol) in THF(10mL) was added dropwise at 0°C to a stirred suspension of zinc dust(1.7g,26mmol) in THF(10mL) which had been activated according to the method described by Knochel (J.O.C. 53,2392,1988). The mixture was left to warm to RT and stir for 3hrs. An aliquot (6.5mmol) of the supernatant containing the benzyl zinc reagent was then added to a stirred solution of **34a**
15 (1.0g,3.85mmol) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (27mg,0.0385mmol) in THF(10mL) at RT under argon. After 1hr a second aliquot (6.5mmol) of the benzyl zinc reagent was added. The resulting black reaction mixture was quenched with 2N HCl (250mL) and extracted with EtOAc (2x100mL). The combined organics were washed with water (50mL) and brine (50mL), filtered through phase separating paper and evaporated to an orange gum. This
20 was chromatographed on SiO_2 (Merck.9385) eluting with 10%EtOAc/i-Hexane to give **34b** as a yellow oil, 590mg(56.6%).

^1H NMR (CDCl_3 ,300MHz) δ 3.9(3H,s, CO_2CH_3);4.48(2H,s, CH_2Ph);7.0-7.5(6H,m);
8.23(1H,m);8.75(1H,m).

MS (ESP $^+$) m/z 270 (M-H) $^+$,210.

25

Compound 34c

- 2N NaOH (2.0mL,4mmol) was added to a solution of **34b** (560mg,2.06mmol) in MeOH (10mL) at RT. After 2hrs the RM was evaporated to remove the MeOH and then partitioned between Et_2O (20mL) and 2N NaOH (20mL). The aqueous was acidified to pH2/3 with 2N
30 HCl and extracted with EtOAc(3x20mL). The combined organics were washed with water

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(20mL) and brine (20mL) ,filtered through phase separating paper and evaporated to yield **34c** as a white solid.453mg(85.3%).

¹H NMR (DMSO-D₆,300MHz) δ4.45(2H,s,CH₂Ph);7.0-7.4(5H,m);
7.55(1H,m);8.3(1H,m);8.53(1H,m).

5 MS (ESP⁺) m/z 256 (M-H)⁺,212.

Compound 34d

34c (630mg,2.45mmol) was coupled with L-Methionine methyl ester hydrochloride (540mg,2.7mmol). (analogously as for the equivalent step in **Example 32**) to give **34d** as a
10 pale yellow solid. 900mg (91.3%).

¹H NMR (DMSO-D₆,250MHz) δ1.9-2.25(5H,m);2.5-2.75(2H+DMSO,m);
3.74(3H,s.CO₂CH₃);4.28(2H,q,CH₂Ph);4.55-4.75(1H,m);7.15-7.5(5H,m);
7.6(1H,m);8.2-8.35(2H,m);9.13(1H,d,NHCO).

MS (ESP⁺) m/z 403 (M+H)⁺.

15

Compound 34e

SnCl₂·2H₂O (2.5g,11.08mmol) was added to a stirred solution of **34d** (900mg,2.24mmol) in EtOAc(50mL) and the resulting mixture heated at reflux for 18hrs.The RM was cooled to RT and treated with 0.88S0 SG NH₃(aq) dropwise to pH8. The resulting heavy white
20 precipitate was removed by filtration through celite(545). The filtrates were then evaporated and purified by chromatography (Mega Bond Elut,SiO₂),eluting with CH₂Cl₂ and then 50%EtOAc/ i-Hexane to give the corresponding aniline **34e**,595mg(71.4%).

¹H NMR (CDCl₃,300MHz) δ1.75-2.2(5H,m);2.25-2.45(2H,m);
3.6-3.8(5H,m,CO₂CH₃+NH₂);4.08(2H,q,CH₂Ph);
25 4.65-4.85(1H,m);6.24(1H,d,NHCO);6.7(1H,m);6.78(1H,m);7.0(1H,m);
7.05-7.3(5H+CHCl₃,m).

MS (ESP⁺) m/z 373 (M+H)⁺,210.

30

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Compound 34f

34e (570mg, 1.53mmol) was coupled with the aldehyde **22b** (580mg, 1.84mmol) (analogously as for the equivalent step in **Example 30**) to give **34f** as a crude pale green foam (1.54g).

5 MS (ESP+) m/z 672 (M+H)⁺.

Compound 34g

34f (1.5g, 2.24mmol) was deprotected (analogously as for the equivalent step in **Example 15**) to give the desired starting material **34g** as a pale brown glass, 550mg

10 (41.9%).

¹H NMR (CDCl₃, 300MHz) δ 1.3-1.65 (10H, m); 1.7-2.2 (5H+H₂O, m); 2.25-2.6 (3H, m); 2.8-3.9 (9H, m); 3.9-4.25 (2H, m); 4.6-4.9 (1H, m); 6.3 (1H, d, NHCO); 6.55-6.8 (2H, m); 6.9-7.4 (5H+CHCl₃, m).

MS (ESP+) m/z 588 (M+H)⁺, 488.

15

b) Preparation of Compound 34h

Starting material **34g** (52mg, 0.087mmol) was hydrolysed (analogously as for the equivalent step in **Example 16**), then purified by reverse phase HPLC (Dynamax® 60A, C₁₈, 8m prep column), eluting with 50% MeOH/H₂O (0.1% TFA) to give **34h** as a

20 colourless glass, 38.2mg (56.6%).

¹H NMR (DMSO-D₆+CD₃COOD, 300MHz) δ 1.5-1.7 (1H, m); 1.8-2.1 (5H+CH₃COOH, m); 2.3-2.6 (3H+DMSO, m); 2.9-3.1 (1H, m); 3.2-4.1 (7H, m); 4.3-4.5 (1H, m); 6.5-6.7 (2H, m); 6.9-7.0 (1H, m); 7.05-7.25 (5H, m).

MS (ESP+) 474 (M+H)⁺.

25 Anal. Calcd for C₂₄H₃₁N₃S₂O₃ 1.4TFA C, 50.8; H, 5.16; N, 6.14

Found C, 51.0; H, 5.3; N, 6.7

The starting material was prepared as described in a) immediately above.

30

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Example 33 (see Scheme 40)

Preparation of

- a) (2S)-2-{2-Benzyl-4-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-benzoylamino}-4-methylsulfanylbutyric acid methyl ester (compound 35) and:
- 5 b) (2S)-2-{2-Benzyl-4-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-benzoylamino}-4-methylsulfanylbutyric acid (compound 35g)

a) Preparation of Compound 35

- The title compound 35 was synthesised from methyl-2-bromo-4-nitro-benzoate using the
- 10 same methodology as described in **Example 32** but using $\text{Pd}_2(\text{dba})_3$ as a source of catalytic palladium in the benzylation reaction.

^1H NMR ($\text{DMSO}-d_6 + \text{CD}_3\text{COOD}$, 300MHz) δ 1.5-1.7(1H,m); 1.8-2.1(5H,m);
 2.3-2.6(3H+DMSO,m); 2.9-3.1(1H,m); 3.2-3.8(8H,m); 4.05(2H,m); 4.4-4.6(1H,m);
 6.4-6.6(2H,m); 7.0-7.35(6H,m)

- 15 MS (ESP+) m/z 488(M+H) $^+$, 325.

Anal Calcd for $\text{C}_{25}\text{H}_{33}\text{N}_3\text{S}_2\text{O}_3 \cdot 2\text{HCl}$ C, 53.6; H, 6.29; N, 7.5

Found C, 53.5; H, 6.5; N, 7.3

b) Preparation of Compound 35g

- 20 Compound 35 (100mg, 0.18mmol; see a) above) was hydrolysed (analogously as for the equivalent step in **Example 32**) to give 35g as a white solid, 85.8mg (67.3%).

^1H NMR ($\text{DMSO}-d_6 + \text{CD}_3\text{COOD}$, 300MHz) δ 1.5-1.7(1H,m); 1.8-2.1(5H,m);
 2.3-2.6(3H+DMSO,m); 2.9-3.9(6H,m); 3.95-4.2(2H,m); 4.3-4.6(1H,m); 6.4-6.5(2H,m);
 7.0-7.3(6H,m)

- 25 MS (ESP+) m/z 474(M+H) $^+$, 325.

Anal Calcd for $\text{C}_{24}\text{H}_{31}\text{N}_3\text{S}_2\text{O}_3 \cdot 1.3\text{TFA}$ C, 51.4; H, 5.24; N, 6.76

Found C, 51.2; H, 5.4; N, 6.7

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Example 34 (see Scheme 41)

(2S)-2-{2-Benzyl-5-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-benzoylamino}-4-methylsulfanylbutyric acid isopropyl ester (compound 36)

The nitro compound **36b** was reduced to the corresponding aniline, coupled with the
 5 thioproline aldehyde **22b** using IPA as solvent and deprotected exactly analogously as for
Example 32 to give the title compound **36**.

¹H NMR (DMSO-D₆+CD₃COOD, 300MHz) δ 1.0-1.3(6H,m); 1.5-1.7(1H,m);
 1.8-2.1(5H,m); 2.3-2.6(3H+DMSO,m); 2.9-4.1(8H,m); 4.3-4.6(1H,m); 4.8-5.0(1H,m);
 6.5-6.7(2H,m); 6.8-7.3(6H,m)

10 MS (ESP+) m/z 516(M+H)⁺, 325.

Anal Calcd for C₂₇H₃₇N₃S₂O₃·2HCl

C, 55.1; H, 6.68; N, 7.14

Found

C, 54.9; H, 7.0; N, 7.1

Compound 36a

A solution of **34d** (25.24g, 62.78mmol) in MeOH (500mL) was treated with 2N NaOH
 15 (35mL, 70mmol). The resulting solution was then evaporated to dryness and the solids
 partitioned between Et₂O (200mL) and water (500mL). The aqueous was then acidified to
 pH2 with 2N HCl and extracted with EtOAc (2x250mL). The combined organics were
 washed with water (2x100mL), brine (100mL), filtered through phase separating paper and
 evaporated to give **36a** as a white solid. 23.57g (96.8%).

20 ¹H NMR (DMSO-D₆, 300MHz) δ 1.8-2.2(5H,m); 2.3-2.6(2H+DMSO,m);
 4.1-4.3(2H,m); 4.4-4.6(1H,m); 7.1-7.3(5H,m); 7.4-7.6(1H,m); 8.1-8.3(2H,m);
 8.9-9.0(1H,m, NHCO)

MS (ESP-) m/z 387(M-H)⁻.

Compound 36b

25 Sulphuryl chloride (5.0mL, 62mmol) was added to a stirred suspension of
36a (19.2g, 50mmol) in IPA (500mL). The resulting mixture was then heated at reflux for
 18hrs. The reaction mixture was then evaporated to 1/5 volume and partitioned between
 EtOAc (1L) and saturated NaHCO₃ (aq) (500mL). The organics were then washed with
 water (200mL), brine (200mL), filtered through phase separating paper and evaporated to
 30 give **36b** as a white solid. 21.25g (100%)

¹H NMR (DMSO-D₆, 300MHz) δ 1.0-1.3(6H,m); 1.8-2.2(5H,m);

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2.3-2.6(2H+DMSO,m);4.1-4.3(2H,m);4.4-4.6(1H,m);4.8-5.0(1H,m);7.1-7.3(5H,m);

7.4-7.6(1H,m);8.1-8.3(2H,m);9.0(1H,m,NHCO)

MS (ESP+) m/z 431(M+H)⁺.

5 Example 35 (see Scheme 42)

(2S)-2-{2-Benzyl-5-[N-([2S,4S]-4-sulfanylpyrrolidin-2-ylmethyl)-N-(3-methoxypropionyl)-amino]-benzoylamino}-4-methylsulfanylbutyric acid isopropyl ester (compound 37)

- 10 Starting material **37b** was deprotected using the same methodology for the equivalent step described in Example 32 to give the title compound **37**.

¹H NMR (DMSO-D₆+CD₃COOD,300MHz) δ1.0-1.3(6H,m);1.5-1.7(1H,m);

1.8-2.1(5H,m);2.2-2.6(5H+DMSO,m);2.9-3.95(10H,m);4.0-4.2(3H,m),

4.4-4.6(1H,m);4.8-5.0(1H,m);7.0-7.5(8H,m)

- 15 MS (ESP+) m/z 602 (M+H)⁺.

Anal Calcd for C₃₁H₄₃N₃S₂O₅·1.5HCl C,56.7;H,6.83;N,6.4

Found C,56.7;H,7.0;N,6.0

The starting material was prepared as follows.

- 20 EEDQ (530mg,2.15mmol) was added to a stirred solution of **36d** (1.5g,2.15mmol; see Example 34) and 3-methoxy propionic acid (220mL, 2.36mmol) in CH₂Cl₂ (15mL). The mixture was left to stir 18hrs at RT then evaporated. The residues were then partitioned between 1N citric acid(aq) (200mL) and EtOAc (100mL). The organics were washed with saturated NaHCO₃ (aq) (50mL), water(50mL) and brine(50mL), filtered through phase
- 25 separating paper and evaporated to give a pale yellow gum. This was then purified by flash chromatography on SiO₂ (Merck 9385) eluting a gradient of 0-50% EtOAc/i-Hexane. Appropriate fractions were filtered and evaporated to give starting material **37b** as a colourless gum.1.14g(67.7%).
- MS (ESP+) m/z 786 (M+H)⁺.

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Example 36 (see Scheme 43)

Preparation of

- a) N-([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-3,3-dimethyl-N-(2-naphthalen-1-yl-ethyl)-butyramide (compound 56) and:
- 5 b) N-([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-N-(2-naphthalen-1-yl-ethyl)-2-pyridin-3-yl-acetamide (compound 57)

a) Preparation of compound 56

The method described in Example 23 for the synthesis of compound (6) was used to

- 10 prepare compound (56) as set out in Scheme 43.

NMR data in CDCl₃ δ 0.91(s, 9H), 1.5(m, 1H), 1.75(m, 1H), 1.82(d, 1H), 1.91(d, 1H), 2.52(m, 1H), 2.92(m, 1H), 3.33(m, 3H), 3.72(m, 4H), 4.15(m, 1H), 7.26(d, 1H), 7.41(t, 1H), 7.56(m, 2H), 7.8(d, 1H), 7.9(2d, 2H), 9.08(br.s, 1H).

Micro Analysis: %Theory C64.2, H7.97, N6.5

- 15 (1.00 HCl . 0.5H₂O %Found C64.4, H7.90, N6.3

Starting material compound (54) was synthesised analogously with Example 23 using the appropriate intermediates:

Compound (52).

- 20 NMR data in CDCl₃ δ 1.00(2s, 9H), 1.46(d, 9H), 1.95(m, 2H), 2.4(m, 2H), 3.3(m, 4H), 3.7(m, 3H), 4.00(m, 3H), 4.57(d, 2H), 5.22(2d, 2H), 5.90(m, 1H), 7.24-8.4(m, 7H).

Compound (54).

NMR data in CDCl₃ δ 1.00(2s, 9H), 1.35(m, 1H), 1.49(s, 9H), 1.89(br.s, 1H), 1.95(d, 1H), 2.3(m, 1H), 2.32(d, 1H), 2.88(2q, 1H), 3.1-3.9(m, 9H), 7.25-8.31(m, 7H).

25

b) Preparation of Compound 57

The method described in Example 24 for the synthesis of compound (27) was used in a similar manner to prepare compound (57).

- NMR data in CDCl₃ δ 1.2(m, 1H), 2.00(m, 1H), 2.6(m, 2H), 3.15-4.40(m, 10H), 7.28-30 8.70(m, 11H), 9.4(br.s, 1H).

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Micro Analysis: %Theory C56.0, H6.20, N8.17
 (2HCl, 2H₂O) %Found C56.4, H6.46, N7.70

Starting material compound(55) was synthesised analogously with Example 24 using

5 appropriate intermediates:

Compound (53).

NMR data in CDCl₃ δ 1.48(s, 9H), 1.84(m, 1H), 2.42(m, 1H), 2.87-3.45(m, 5H), 3.63-4.26(m, 7H), 4.55(d, 2H), 5.22(2d, 2H), 5.9(m, 1H), 7.1-8.7(m, 11H).

Compound (55).

10 NMR data in CDCl₃ δ 1.34(m, 1H), 1.5(s, 9H), 1.95(m, 1H), 2.32(m, 2H), 2.72-4.00(m, 10H), 7.1-8.6(m, 11H).

Example 37 (see Scheme 44)

Preparation of

- 15 a) **N-(2,2-Diphenyl-ethyl)-N-([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-3-methyl-butylamide** (compound 67);
 b) **N-(2,2-Diphenyl-ethyl)-N-([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-3,3-dimethyl-butylamide** (compound 68);
 c) **N-(2,2-Diphenyl-ethyl)-N-([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-2-pyridin-3-yl-acetamide** (compound 69) and;
 20 d) **N-(2,2-Diphenyl-ethyl)-1-oxy-N-([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-6-methoxy-nicotinamide** (compound 70).

a) Preparation of Compound 67

- 25 The method described in Example 23 for the synthesis of compound (6) was used in an analogous manner to prepare compound (67) using appropriate intermediates - see Scheme 44.

NMR data in DMSO-d₆ δ 0.75(m, 6H), 1.55(m, 1H), 1.87(m, 2H), 2.05-2.45(m, 1H), 3.05(m, 1H), 3.25-3.70(m, 6H), 4.05(m, 2H), 4.20-4.55(m, 1H), 7.30(m, 10H), 8.80-

30 9.80(2br.s, 2H)

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Micro Analysis: %Theory C63.9, H7.82, N6.21

(1.00HCl, 1.00H₂O) %Found C64.1, H7.70, N6.00

Compound (58).

NMR data in CDCl₃ δ 1.50(s, 9H), 1.77(m, 1H), 2.40(m, 1H), 2.75(m, 1H), 3.00(m, 1H),

- 5 3.14(q, 1H), 3.24(d, 2H), 3.67(m, 1H), 3.93(m, 1H), 4.10(m, 2H), 4.54(d, 2H), 5.25(m, 2H),
5.90(m, 1H), 7.25(m, 10H)

Compound (59).

NMR data in CDCl₃ δ 0.85(m, 6H), 1.48(m, 9H), 1.80(m, 2H), 2.10(m, 2H), 2.40(m, 1H),

2.80-4.35(m, 9H), 4.55(m, 2H), 5.25(m, 2H), 5.90(m, 1H), 7.25(m, 10H)

- 10 Compound (63).

NMR data in CDCl₃ δ 0.85(2d, 6H), 1.24(m, 1H), 1.48(s, 9H), 1.68(m, 1H), 1.81(d, 1H),

1.95-2.35(m, 3H), 2.75-3.65(m, 6H), 3.90-4.55(m, 3H), 7.25(m, 10H)

b) Preparation of Compound 68

- 15 Similarly compound (68) was synthesised from compound (60) as set out in Scheme 44.

Compound (68)

NMR data in DMSO-d₆ δ 0.85(m, 9H), 1.55(m, 1H), 1.74-2.27(m, 2H), 2.37(m, 1H),

3.05(m, 1H), 3.45(m, 6H), 4.05(m, 2H), 4.18-4.55(m, 1H), 7.28(m, 10H), 8.90-9.90(m, 2H)

Micro Analysis: %Theory C64.6, H8.02, N6.02

- 20 (1.0HCl, 1.0H₂O) %Found C64.8, H8.30, N5.70

Compound (60).

NMR data in CDCl₃ δ 0.93(m, 9H), 1.50(s, 9H), 1.82(m, 2H), 2.35(m, 3H), 2.90-4.35(m,

8H), 4.55(m, 2H), 5.25(m, 2H), 5.90(m, 1H), 7.25(m, 10H).

Compound (64).

- 25 NMR data in CDCl₃ δ 0.93(s, 9H), 1.24(m, 1H), 1.48(s, 9H), 1.80(q, 1H), 2.23(d, 1H),
2.30(m, 1H), 2.75-3.70(m, 6H), 3.90-4.60(m, 3H), 7.25(m, 10H).

c) Preparation of Compound 69

Compound (69) was synthesised from compound (61) (see Scheme 44) analogously with

- 30 the procedure described in Example 24 for the preparation of compound (27).

Compound (69).

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NMR data in CDCl_3 δ 1.95(m,1H), 2.40(m,1H), 2.60(m,1H), 3.15-4.50(m,11H),
7.28(m,10H), 7.67(m,1H), 8.05(m,1H), 8.50(m,1H), 8.71(m,1H), 9.10-10.20(br.d, 2H).

Micro Analysis: %Theory C55.1, H5.51, N7.01

(2.0 HCl,0.75TFA,0.5H₂O) %Found C55.0, H5.60, N6.90

5 Compound (61).

NMR data in CDCl_3 δ 1.47(s, 9H), 1.80(m,1H), 2.30-4.65(m,14H), 5.23(m, 2H).

5.90(m,1H), 7.25(m,12H), 8.10-8.55(m, 2H).

Compound (65).

NMR data in CDCl_3 δ 1.25(m,1H), 1.48(s, 9H), 2.30(m,1H), 2.70-4.55(m,12H).

10 7.30(m,12H), 8.28(2d,1H), 8.45(m,1H).

d) Preparation of Compound 70

Similarly compound (70) was synthesised from compound (62) using appropriate intermediates.

15 NMR data in CDCl_3 δ 1.67(m,1H), 2.15(d,1H), 2.47(m,1H), 3.16(br.s, 1H), 3.50(m, 2H),
3.85-4.40(m, 8H), 5.22(br.s,1H), 6.56(d,1H), 7.00-7.35(m,11H), 7.90(s,1H), 8.85-
10.75(2br.s, 2H)

Micro Analysis %Theory C57.2, H5.91, N7.70

(2.0HCl,0.5H₂O) %Found C57.5, H5.60, N7.30

20

Compound (62).

NMR data in CDCl_3 δ 1.50(s, 9H), 1.60(m,1H), 2.47(m,1H), 3.00-4.50(m,12H), 4.58(d,
2H), 5.25(m, 2H), 5.90(m,1H), 6.53(d,1H), 6.95(m,1H), 7.25(m,11H).

Compound (66).

25 NMR data in CDCl_3 δ 1.20(m,1H), 1.45(s, 9H), 2.30(m,1H), 2.66(m,1H), 3.00-3.45(m,
4H), 3.55(m,1H), 3.95-4.25(m, 5H), 4.47(m,1H), 6.55(d,1H), 7.25(m,11H), 7.65(m,1H).

Example 38 (see Scheme 45)

Preparation of

30 a) N-([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-3-methyl-N-(2-naphthalen-2-yl-ethyl)-butyramide (compound 80);

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- b) N-([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-3,3-dimethyl-N-(2-naphthalen-2-yl-ethyl)-butyramide (compound 81);
- c) N-([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-N-(2-naphthalen-2-yl-ethyl)-2-pyridin-3-yl-acetamide (compound 82) and;
- 5 d) N-([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-2-(4-methoxy-phenyl)-N-(2-naphthalen-2-yl-ethyl)-acetamide (compound 83).

a) Preparation of Compound 80

The method described in Example 23 for the synthesis of compound (6) was used to
10 prepare compound (80).

NMR data in DMSO-d₆ δ 0.75(m, 6H), 0.87(d, 1H), 1.65(m, 1H), 1.92(m, 1H), 2.02(d, 1H), 3.03(m, 3H), 3.20-3.80(m, 9H), 7.48(m, 3H), 7.75(d, 1H), 7.85(m, 3H), 8.90-9.90(br.d, 2H)

15 Micro Analysis: %Theory C64.9, H7.68, N6.88
(1.00 HCl) %Found C64.9, H7.50, N6.80

Starting material compound (76) was synthesised analogously with Example 23 using appropriate intermediates - see Scheme 45.

20

Compound (71).

NMR data in CDCl₃ δ 1.50(s, 9H), 1.85(m, 1H), 2.50(m, 1H), 2.80(m, 1H), 3.00(m, 5H), 3.20(m, 1H), 3.65(m, 1H), 4.00(m, 1H), 4.10(m, 1H), 4.53(d, 2H), 5.20(m, 2H), 5.90(m, 1H), 7.32(m, 1H), 7.42(m, 2H), 7.63(s, 1H), 7.80(m, 3H).

25

Compound (72).

NMR data in CDCl₃ δ 0.90(m, 7H), 1.00-2.60(m, 14H), 3.00(m, 2H), 3.10-4.20(m, 7H), 4.60(m, 2H), 5.25(m, 2H), 5.90(m, 1H), 7.30-7.50(m, 3H), 7.60(m, 1H), 7.80(m, 3H).

30

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Compound (76).

NMR data in CDCl_3 δ 0.90(m, 6H), 1.10-2.50(m, 15H), 2.80-3.80(m, 9H), 7.26-7.50(m, 3H), 7.60(m, 1H), 7.80(m, 3H)

5 b) Preparation of Compound 81

Compound (81) was synthesised from compound (73) as set out in Scheme 45 in a similar manner to preparation of compound 80 (see above).

NMR data in DMSO-d_6 δ 1.08(d, 9H), 1.80(m, 1H), 2.15(m, 2H), 2.65(m, 1H), 3.00-10 4.00(m, 10H), 7.63(m, 3H), 7.90(s, 1H), 8.03(m, 3H), 9.50(br.d, 2H).

Micro Analysis: %Theory C64.9, H7.93, N6.58

(1.0HCl, 0.25H₂O) %Found C64.8, H8.10, N6.50

Compound (73).

15 NMR data in CDCl_3 δ 1.00(m, 9H), 1.47(s, 9H), 1.80-2.55(m, 4H), 3.00(m, 2H), 3.10-4.20(m, 8H), 4.60(d, 2H), 5.25(m, 2H), 5.90(m, 1H), 7.30-7.85(m, 7H)

Compound (77).

NMR data in DMSO-d_6 (100°C) δ 0.95(m, 9H), 1.35-1.75(m, 9H), 2.15(s, 2H), 20 2.40(m, 1H), 2.60-3.90(m, 12H), 7.40(m, 3H), 7.70(m, 1H), 7.80(m, 3H).

c) Preparation of Compound 82

Compound (82) was synthesised from compound (74) as set out in Scheme 45 by a similar procedure to that described in Example 24 for the preparation of compound (27).

25

Compound (82).

NMR data in DMSO-d_6 δ 1.65(m, 1H), 2.90-4.15(m, 14H), 7.35-8.90(m, 11H), 9.50(br.d, 2H).

30 Micro Analysis: %Theory C51.9, H5.19, N6.99

(2.0HCl, 1.0TFA, 0.5H₂O) %Found C52.2, H5.40, N.7.00

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Compound (74).

NMR data in DMSO-d₆ (100°C) δ 1.45-1.75(m,10H), 2.85-3.85(m,11H), 4.03(m,1H), 4.20(m,1H), 4.45-4.65(m, 2H), 5.20(m, 2H), 5.90(m,1H), 7.23(m,1H), 7.45(m, 4H), 7.67(s,1H), 7.80(m, 3H), 8.35(m, 2H).

5

Compound (78)

NMR data in DMSO-d₆ (100°C) δ 1.30-1.75(m, 9H), 2.40(m,1H), 2.55-3.90(m,14H), 7.10-8.45(m,11H).

10 d) Preparation of Compound 83

Similarly compound (83) was synthesised from compound (75) using appropriate intermediates as set out in Scheme 45.

Compound (85).

15 NMR data in DMSO-d₆ δ 1.65(m,1H), 2.95(m, 2H), 3.08(m,1H), 3.25-4.00(m,13H), 6.80(m, 2H), 7.06(2d, 2H), 7.47(m, 3H), 7.68(d,1H), 7.85(m, 3H), 9.35(br.d. 2H).

Micro Analysis:	%Theory C62.7, H6.57, N5.62
(1.5 HCl,0.5H ₂ O)	%Found C62.4, H6.50, N5.40

20

Compound (75).

NMR data in DMSO-d₆ (100°C) δ 1.45(s, 9H), 1.75(m,1H), 2.75-3.85(m,14H), 4.00(m,1H), 4.14(m,1H), 4.45-4.65(m, 2H), 5.20(m, 2H), 5.90(m,1H), 6.80(m, 2H), 7.05(m, 2H), 7.33(m,1H), 7.45(m, 2H), 7.63(s,1H), 7.80(m, 3H).

25

Compound (79).

NMR data in DMSO-d₆ (100°C) δ 1.30-1.75(m, 9H), 2.35(m,1H), 2.60-3.90(m,17H), 6.78(m, 2H), 7.05(m, 2H), 7.40(m, 3H), 7.65(m,1H), 7.80(m, 3H).

30

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Example 39 (see scheme 46)

Preparation of

a) (2S)-2-({2-phenyl-4-[(2S,4S)-4-sulfanyl-pyrrolidin-2-ylmethyl]-amino}-phenylcarbonyl)-amino-4-methylsulfanyl-butyric acid methyl ester (compound 38)

5 and;

b) (2S)-2-({2-phenyl-4-[(2S,4S)-4-sulfanyl-pyrrolidin-2-ylmethyl]-amino}-phenylcarbonyl)-amino-4-methylsulfanyl-butyric acid (compound 38f).

a) Preparation of Compound 38

Methyl -2-bromo-4-nitro-benzoate was coupled with phenyl boronic acid (analogously as

10 for the equivalent step in **Example 30**) then coupled and deprotected using the same methodology as previously described for **Example 32** to give the title compound **38**.

¹H NMR (DMSO-D₆, 250MHz) δ 1.35-1.75(3H,m); 1.8(3H,s); 1.9-2.2(2H,m); 2.25-2.5(2H+DMSO,m); 2.75-3.9(10H,m); 4.0-4.25(1H,m); 5.0-5.9(5H.bs, H₂O); 6.3-6.6(2H,m); 7.0-7.3(7H,m); 7.95(1H,m); 9.2-9.8(2H.bd).

15 MS (ESP+) m/z 474 (M+H)⁺. 311.196.

Anal. Calcd for C₂₄H₃₁N₃O₃S₂.2HCl.1.5H₂O C, 50.3; H, 6.3; N, 7.3

Found C, 50.4; H, 6.1; N, 7.3

b) Preparation of Compound 38f

20 Compound **38** was hydrolysed to the corresponding acid (analogously as for the equivalent step in **Example 33**) to give 38f.

¹H NMR (DMSO-D₆+CD₃COOD, 300MHz) δ 1.5-1.9(3H+CD₃COOD,m); 1.95(3H,s); 2.05-2.35(2H,m); 2.4-2.6(2H+DMSO,m); 3.0-3.1(1H,m); 3.2-3.9(4H,m); 4.2-4.3(1H,m); 6.5-6.7(2H,m); 7.2-7.4(6H,m).

25 MS (ESP+) m/z 460 (M+H)⁺. 311.

Anal. Calcd for C₂₃H₂₉N₃O₃S₂.1.35TFA C, 50.3; H, 4.99; N, 6.85

Found C, 50.2; H, 5.1; N, 6.8

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Example 40**Pharmaceutical compositions**

The following illustrate representative pharmaceutical dosage forms of the invention as defined herein (the active ingredient being termed "Compound X"). for
5 therapeutic or prophylactic use in humans:

(a)	<u>Tablet I</u>	<u>mg/tablet</u>
	Compound X.....	100
	Lactose Ph.Eur.....	182.75
10	Croscarmellose sodium.....	12.0
	Maize starch paste (5% w/v paste).....	2.25
	Magnesium stearate.....	3.0
(b)	<u>Tablet II</u>	<u>mg/tablet</u>
15	Compound X.....	50
	Lactose Ph.Eur.....	223.75
	Croscarmellose sodium.....	6.0
	Maize starch.....	15.0
	Polyvinylpyrrolidone (5% w/v paste).....	2.25
20	Magnesium stearate.....	3.0
(c)	<u>Tablet III</u>	<u>mg/tablet</u>
	Compound X.....	1.0
	Lactose Ph.Eur.....	93.25
25	Croscarmellose sodium.....	4.0
	Maize starch paste (5% w/v paste).....	0.75
	Magnesium stearate.....	1.0

30

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	(d)	<u>Capsule</u>	<u>mg/capsule</u>
		Compound X.....	10
		Lactose Ph.Eur.....	488.5
		Magnesium.....	1.5
5			
	(e)	<u>Injection I</u>	<u>(50 mg/ml)</u>
		Compound X.....	5.0% w/v
		1M Sodium hydroxide solution.....	15.0% v/v
		0.1M Hydrochloric acid	
10		(to adjust pH to 7.6)	
		Polyethylene glycol 400.....	4.5% w/v
		Water for injection to 100%	
	(f)	<u>Injection II</u>	<u>(10 mg/ml)</u>
15		Compound X.....	1.0% w/v
		Sodium phosphate BP.....	3.6% w/v
		0.1M Sodium hydroxide solution.....	15.0% v/v
		Water for injection to 100%	
20	(g)	<u>Injection III</u>	<u>(1 mg/ml, buffered to pH6)</u>
		Compound X.....	0.1% w/v
		Sodium phosphate BP.....	2.26% w/v
		Citric acid.....	0.38% w/v
		Polyethylene glycol 400.....	3.5% w/v
25		Water for injection to 100%	
	(h)	<u>Aerosol I</u>	<u>mg/ml</u>
		Compound X.....	10.0
		Sorbitan trioleate.....	13.5
30		Trichlorofluoromethane.....	910.0
		Dichlorodifluoromethane.....	490.0

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5	(i)	<u>Aerosol II</u>	<u>mg/ml</u>
		Compound X.....	0.2
		Sorbitan trioleate.....	0.27
		Trichlorofluoromethane.....	70.0
		Dichlorodifluoromethane.....	280.0
		Dichlorotetrafluoroethane.....	1094.0
10	(j)	<u>Aerosol III</u>	<u>mg/ml</u>
		Compound X.....	2.5
		Sorbitan trioleate.....	3.38
		Trichlorofluoromethane.....	67.5
		Dichlorodifluoromethane.....	1086.0
		Dichlorotetrafluoroethane.....	191.6
15	(k)	<u>Aerosol IV</u>	<u>mg/ml</u>
		Compound X.....	2.5
		Soya lecithin.....	2.7
		Trichlorofluoromethane.....	67.5
		Dichlorodifluoromethane.....	1086.0
20		Dichlorotetrafluoroethane.....	191.6
25	(l)	<u>Ointment</u>	<u>ml</u>
		Compound X.....	40 mg
		Ethanol.....	300 µl
		Water.....	300 µl
		1-Dodecylazacycloheptan-2-one.....	50 µl
		Propylene glycol.....	to 1 ml

Note

30 The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means.

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for example to provide a coating of cellulose acetate phthalate. The aerosol formulations (h)-(k) may be used in conjunction with standard, metered dose aerosol dispensers, and the suspending agents sorbitan trioleate and soya lecithin may be replaced by an alternative suspending agent such as sorbitan monooleate, sorbitan sesquioleate, polysorbate 80.

5 polyglycerol oleate or oleic acid.

Example 41 (see Scheme 47)

Preparation of

- a) (2S)-4-Carbamoyl-2-({2-phenyl-5-[(2S,4S)-4-sulfanyl-pyrrolidin-2-ylmethyl]-
10 amino]-phenylcarbonyl}-amino)-butyric acid (compound 39e); and
b) (2S)-4-Carbamoyl-2-({2-phenyl-5-[(2S,4S)-4-sulfanyl-pyrrolidin-2-ylmethyl]-
amino]-phenylcarbonyl}-amino)-butyric acid methyl ester (compound 39)

a) Preparation of Compound 39

15 Compound 39a

32a (1.5g, 6.2mmol) was coupled with L-Glutamine methyl ester (analogously as for the equivalent step in **Example 30**) to give compound **39a** as a white solid, 1.2g (50.5%)
MS (ESP)+ m/z 386 (M+H)+.

Compound 39

- 20 **39a** was reduced, coupled with the aldehyde (**22b**) and selectively deprotected using the same methodology as previously described for **Example 32** to give the title compound **39**.
MS (ESP+) m/z 471 (M+H)+.

Anal. Calcd for C₂₄H₃₀N₄O₄S, 3HCl, 0.25H₂O C, 49.3; H, 5.8; N, 9.6

Found C, 49.2; H, 5.9; N, 9.2

25 b) Preparation of Compound 39e

39 was hydrolysed (analogously as for the equivalent step in **Example 32**) to give the title compound **39e**.

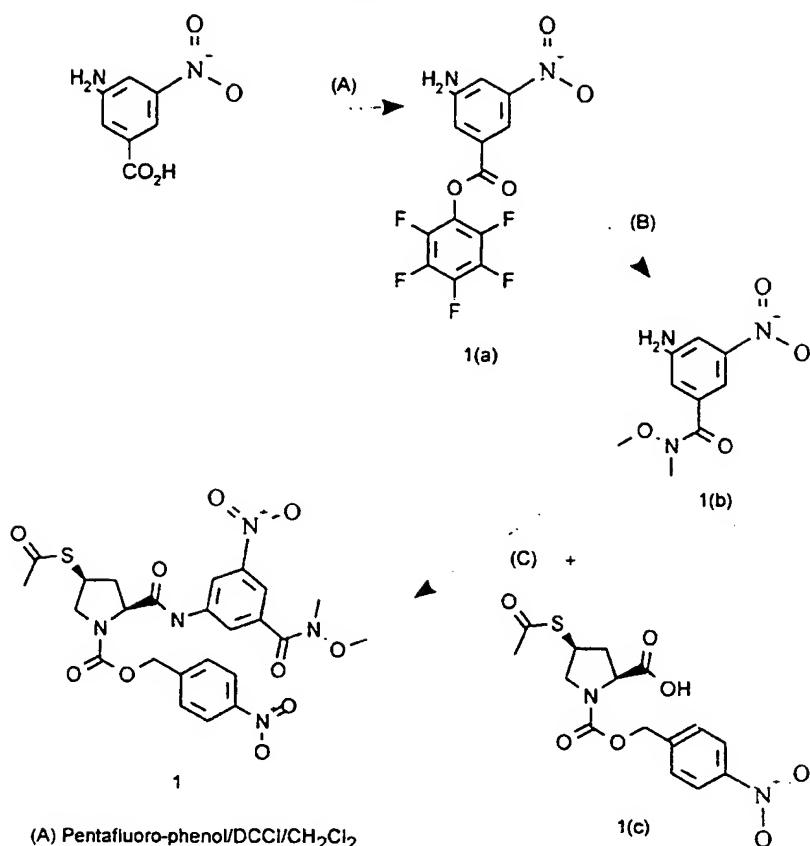
MS (ESP-) m/z 455 (M-H)-.

Anal. Calcd for C₂₃H₂₈N₄O₄S, 2TFA C, 47.4; H, 4.4; N, 8.2

- 30 Found C, 47.0; H, 4.5; N, 7.9

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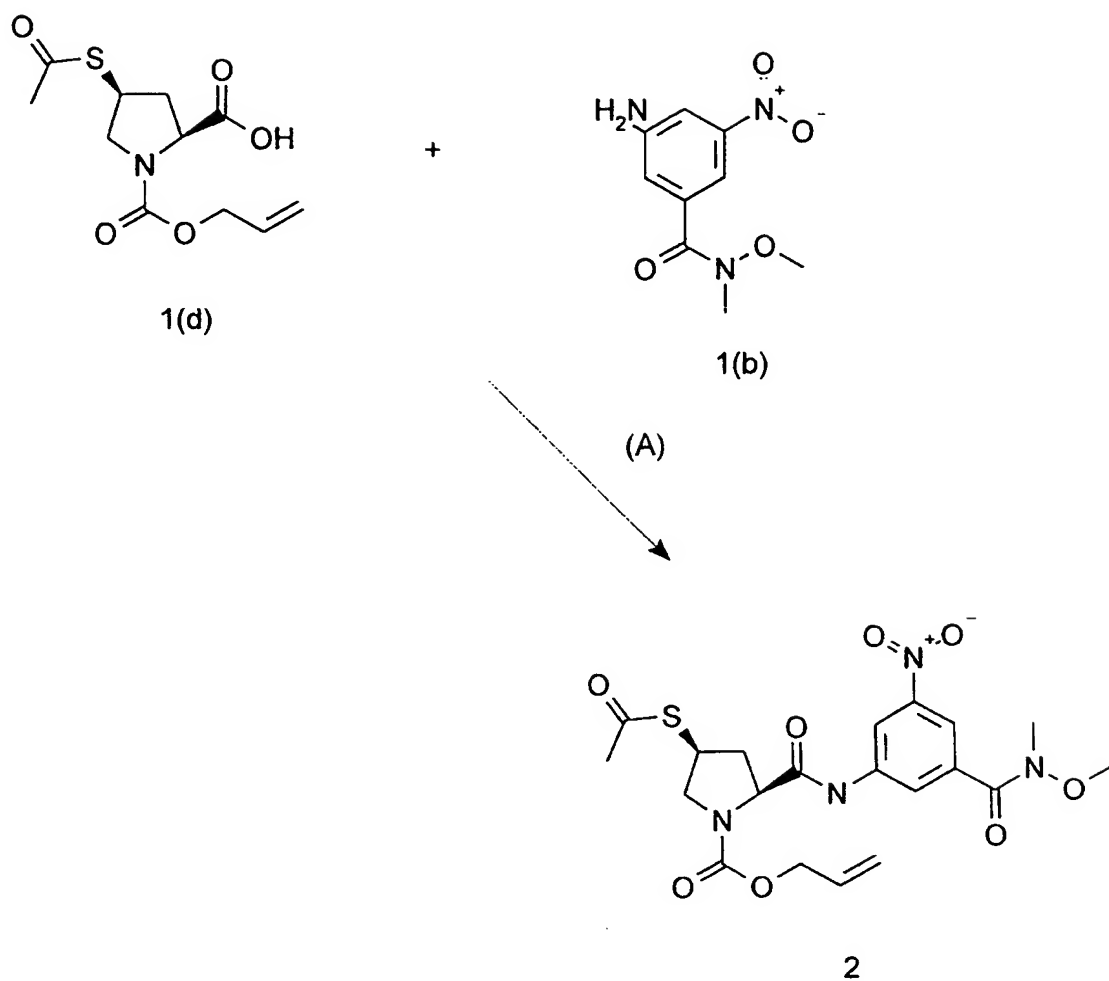
Scheme 1



SUBSTITUTE SHEET (RULE 26)

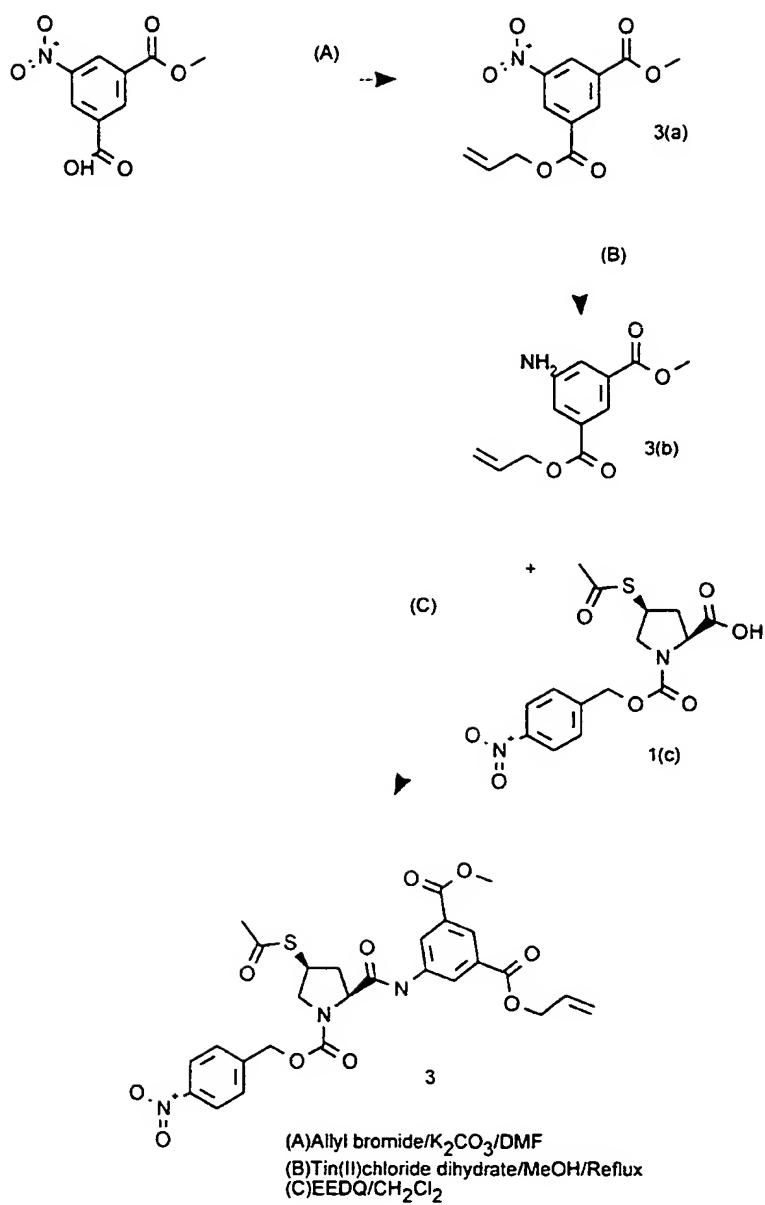
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Scheme 2

(A) EEDQ/CH₂Cl₂

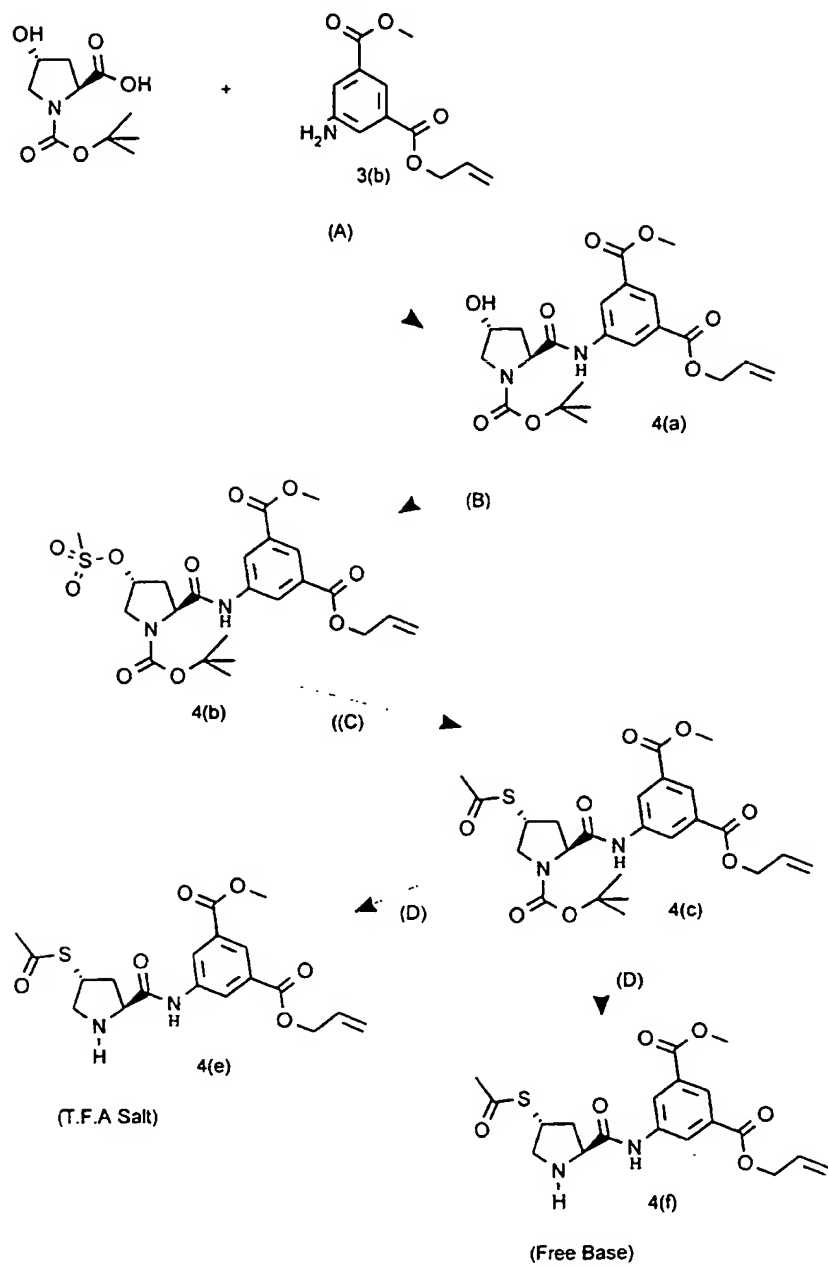
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Scheme 3



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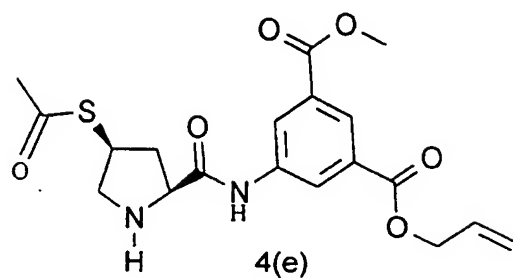
Scheme 4



SUBSTITUTE SHEET (RULE 26)

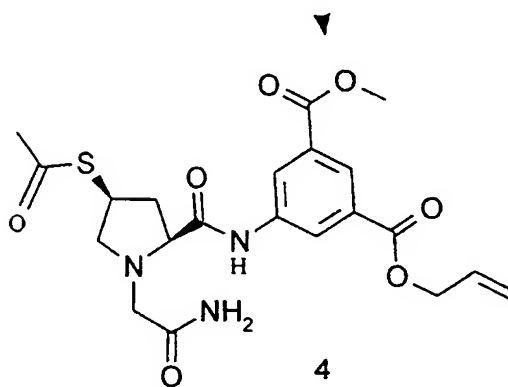
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Scheme 4 cont.



(T.F.A. salt)

(E)

(A) EEDQ/CH₂Cl₂(B) Methanesulphonyl chloride/triethylamine/CH₂Cl₂

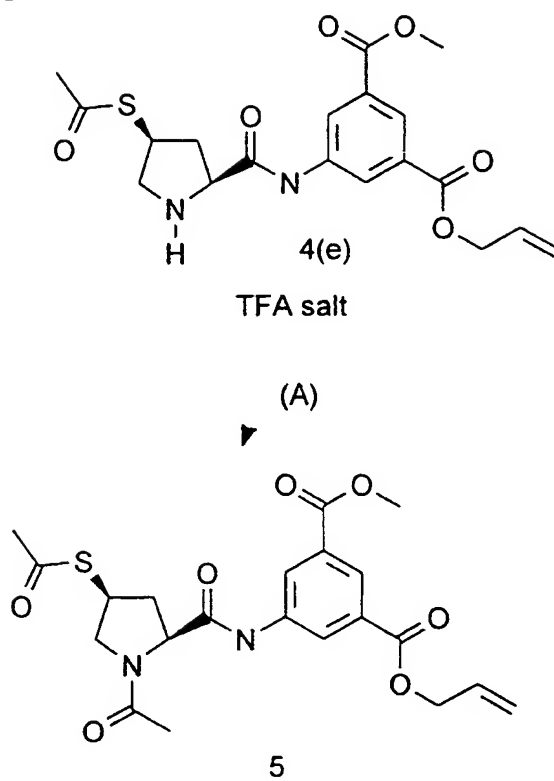
(C) Potassium thioacetate/acetone

(D) T.F.A.

(E) Iodoacetamide/Sodium Bicarbonate/DMF

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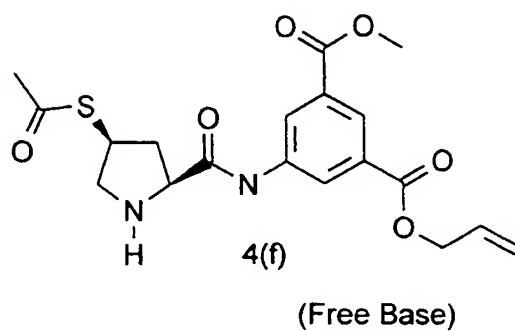
Scheme 5



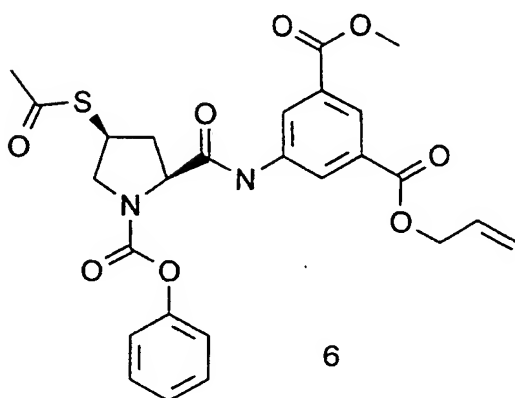
(A) Acetic anhydride/triethylamine/ CH_2Cl_2

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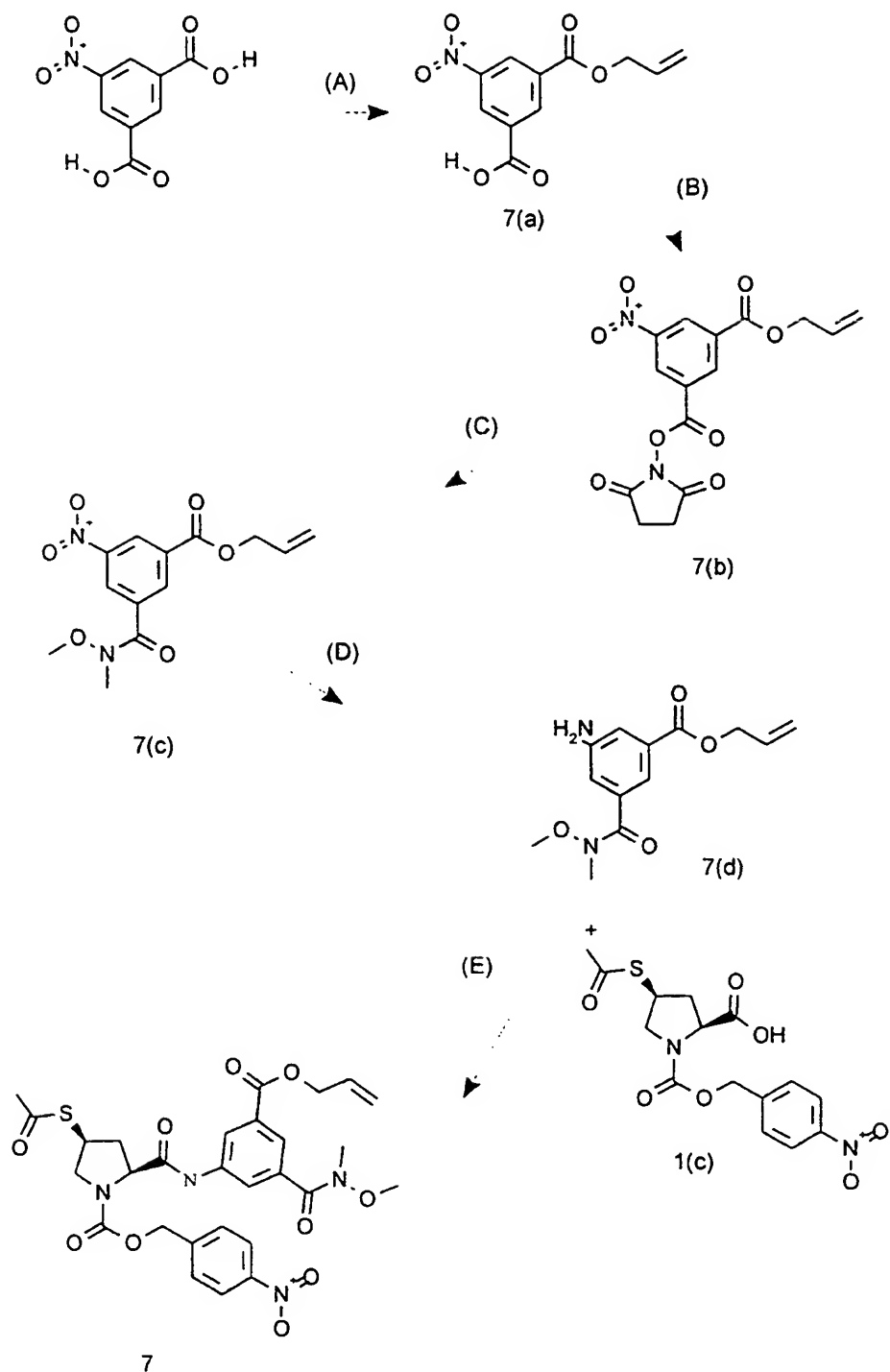
Scheme 6



(A)

(A)Phenyl chloroformate/triethylamine/ CH_2Cl_2

Scheme 7



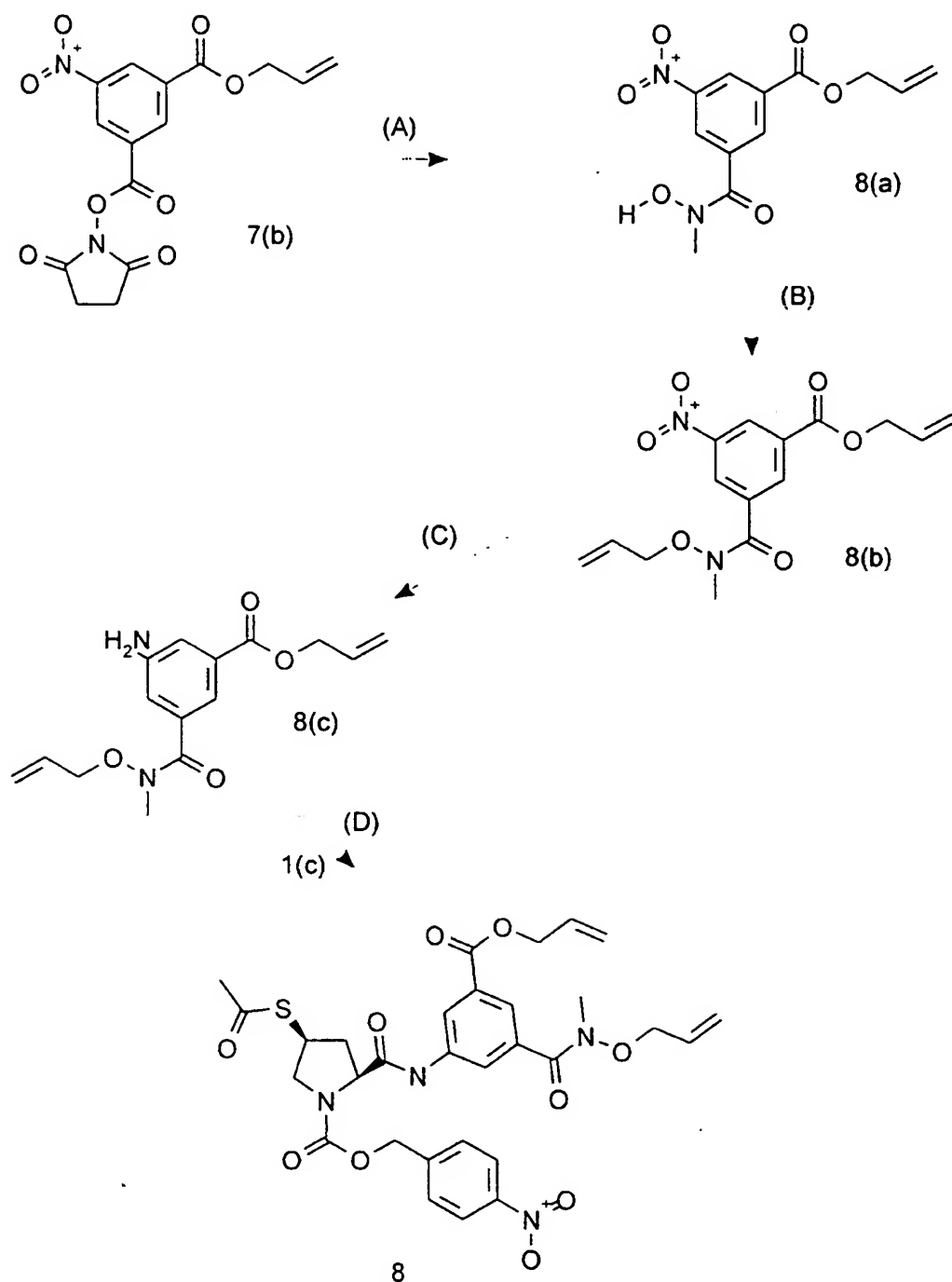
- 114 -

Scheme 7(cont.)

- (A) Allyl bromide/potassium carbonate/DMA/90deg./4hrs
(B) DCCl/CH₂Cl₂/N-Hydroxysuccinimide/R.T./3.5hrs.
(C) N,O-Dimethylhydroxylamine HCl/Triethylamine/5deg./16hrs.
(D) Tin(II)Chloride/Methanol/Reflux/1hr
(E) EEDQ/CH₂Cl₂/R.T./16hrs.

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Scheme 8



(A) N-Methylhydroxylamine HCl./Triethylamine/ CH_2Cl_2 /5deg./16hrs.

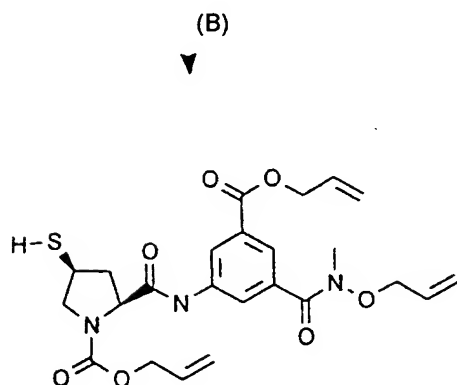
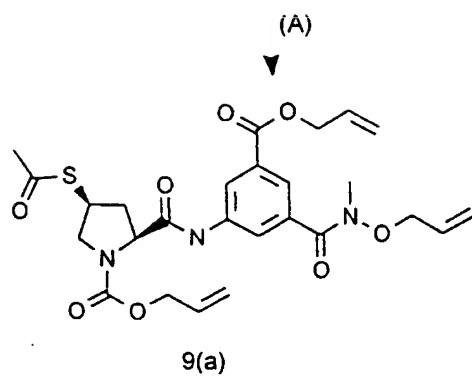
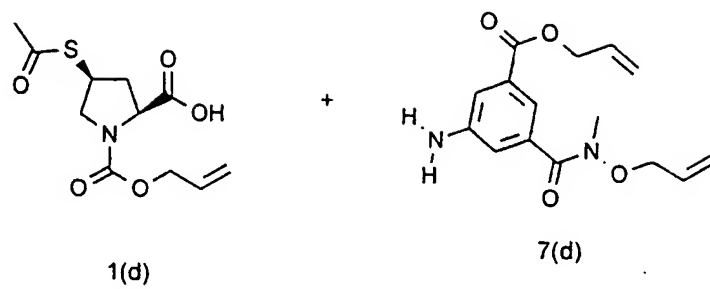
(B) Allyl bromide/Potassium carbonate/R.t./DMF/3hrs.

(C) Tin(II) chloride/Ethyl acetate/70Deg.

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Scheme 9



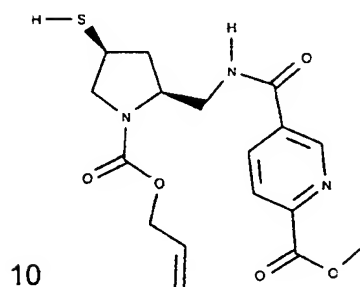
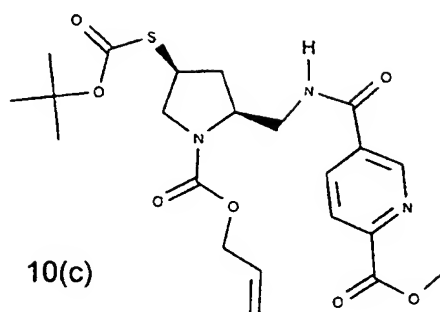
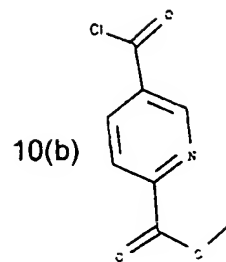
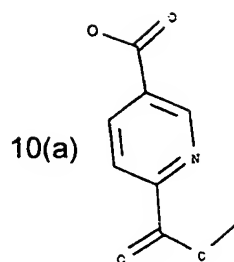
9

(A) EEDQ/CH₂Cl₂

(B) 0.1M Sodium hydroxide/Allyl alcohol/R.t.

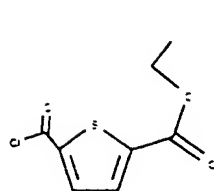
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SCHEME 10

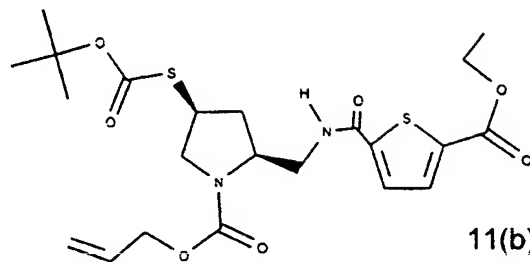


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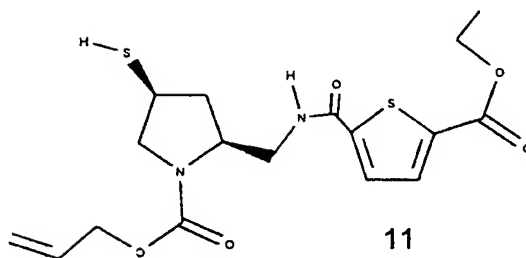
SCHEME 11



11(a)



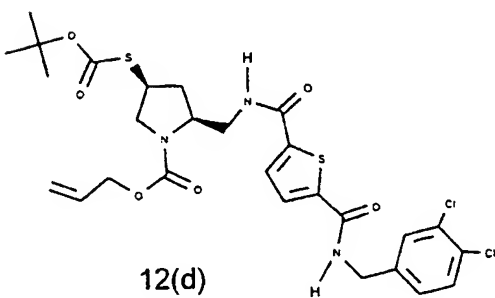
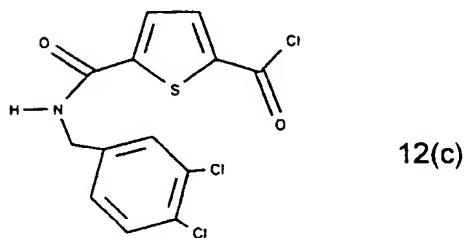
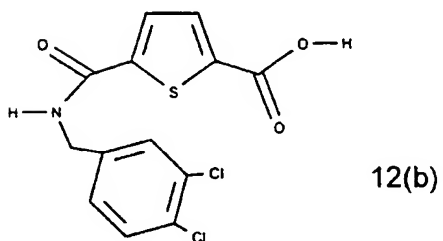
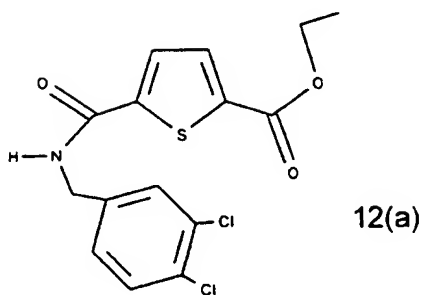
11(b)



11

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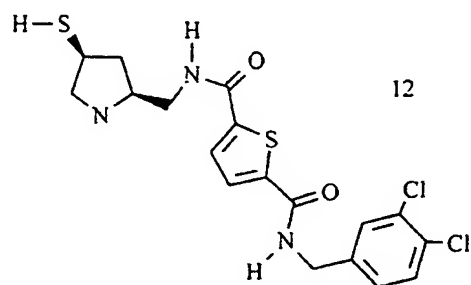
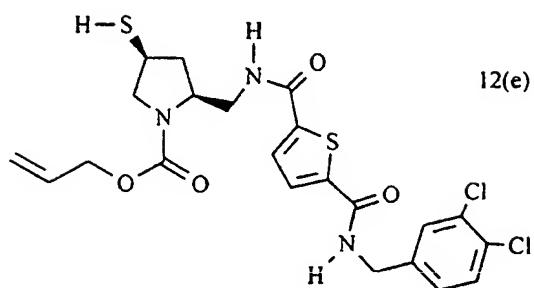
SCHEME 12



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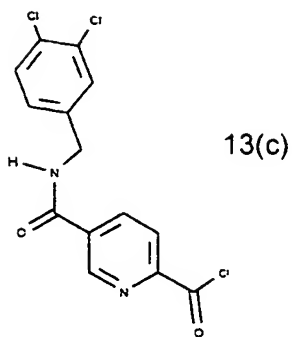
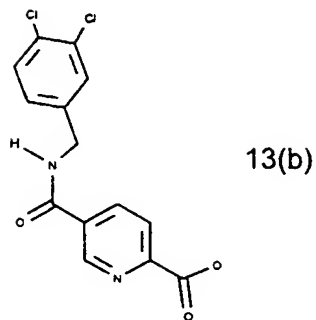
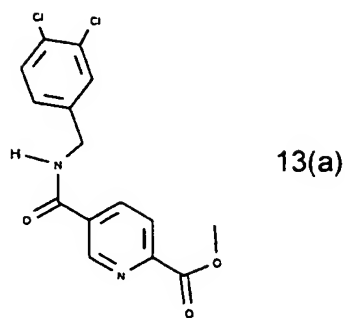
SCHEME 12 (Cont'd)



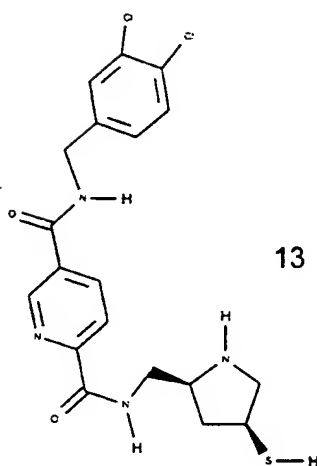
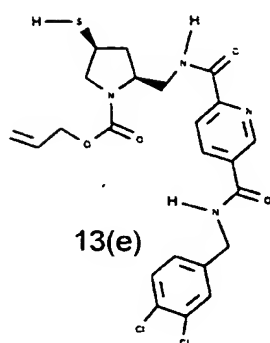
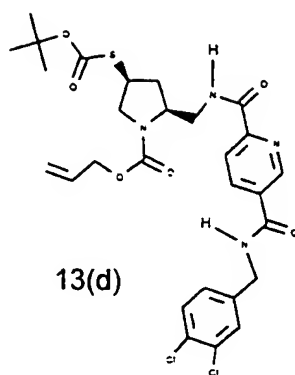
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SCHEME 13

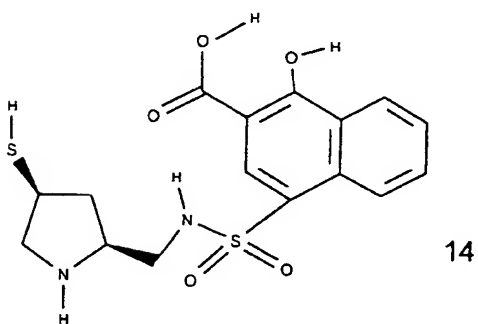
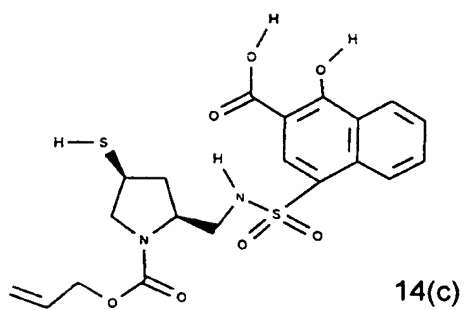
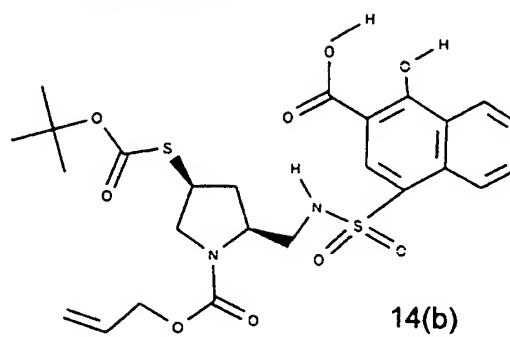
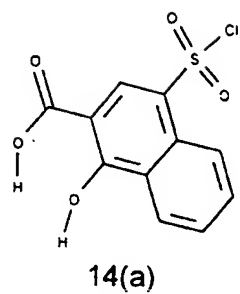


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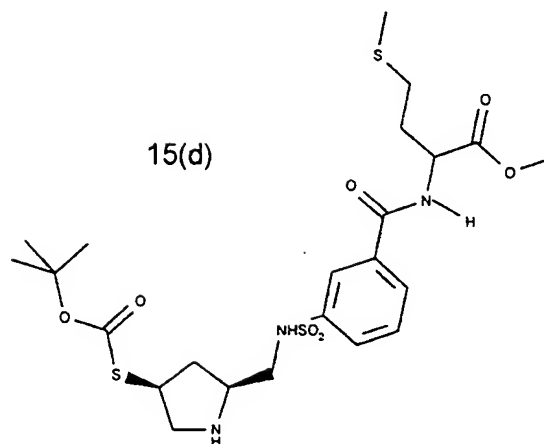
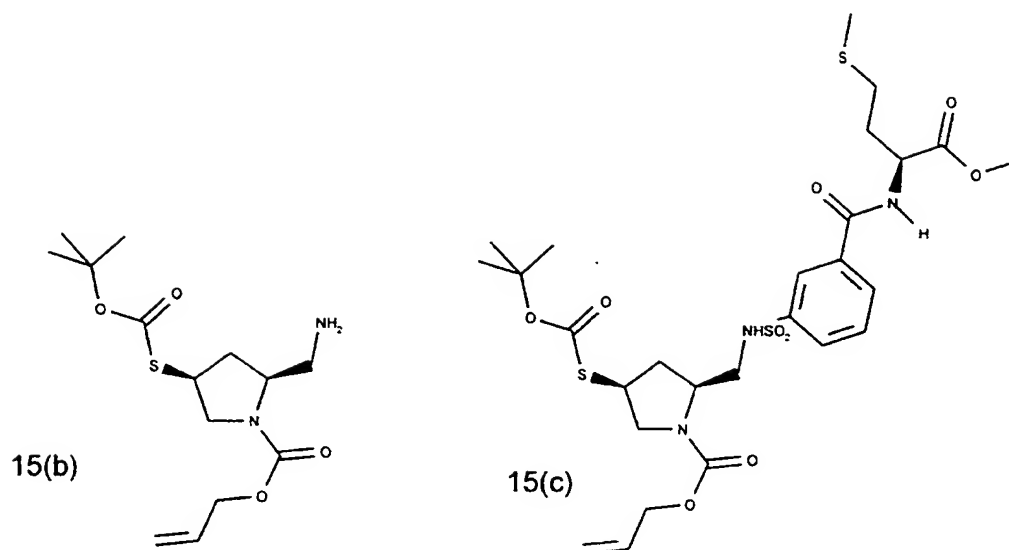
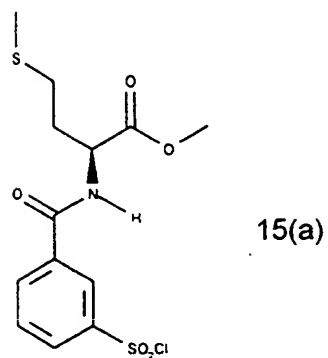
SCHEME 14



SUBSTITUTE SHEET (RULE 26)

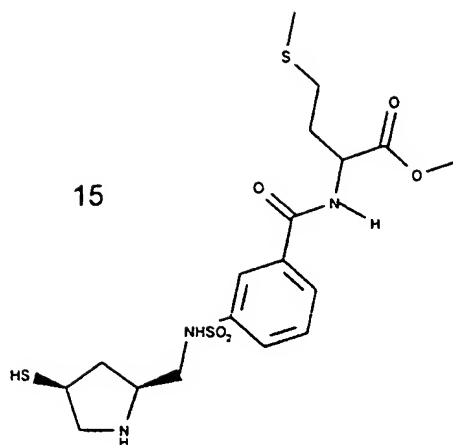
- 124 -

SCHEME 15



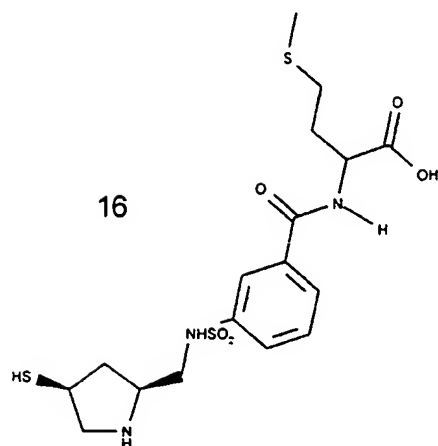
SUBSTITUTE SHEET (RULE 26)

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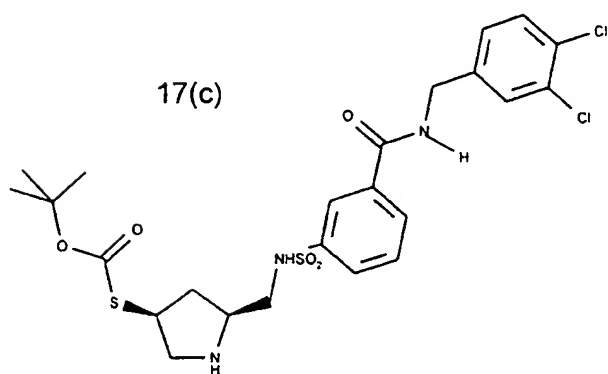
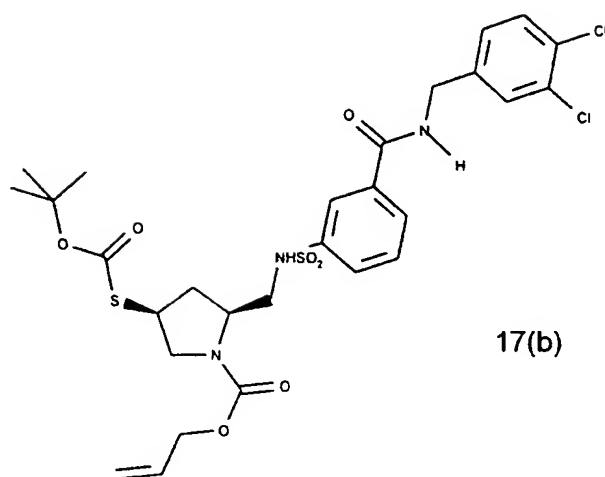
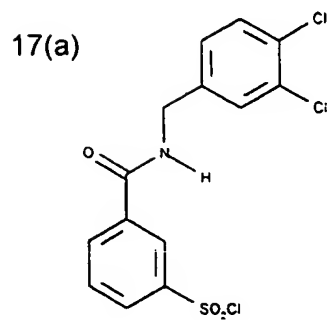
- 126 -

SCHEME 16



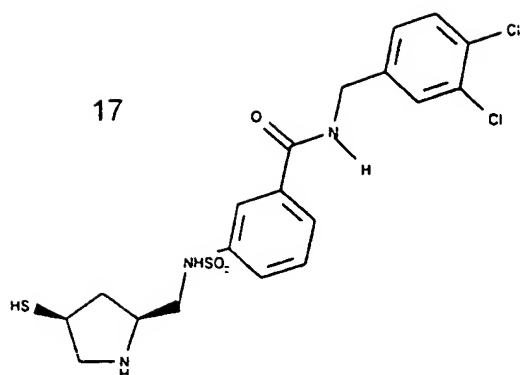
- 127 -

SCHEME 17



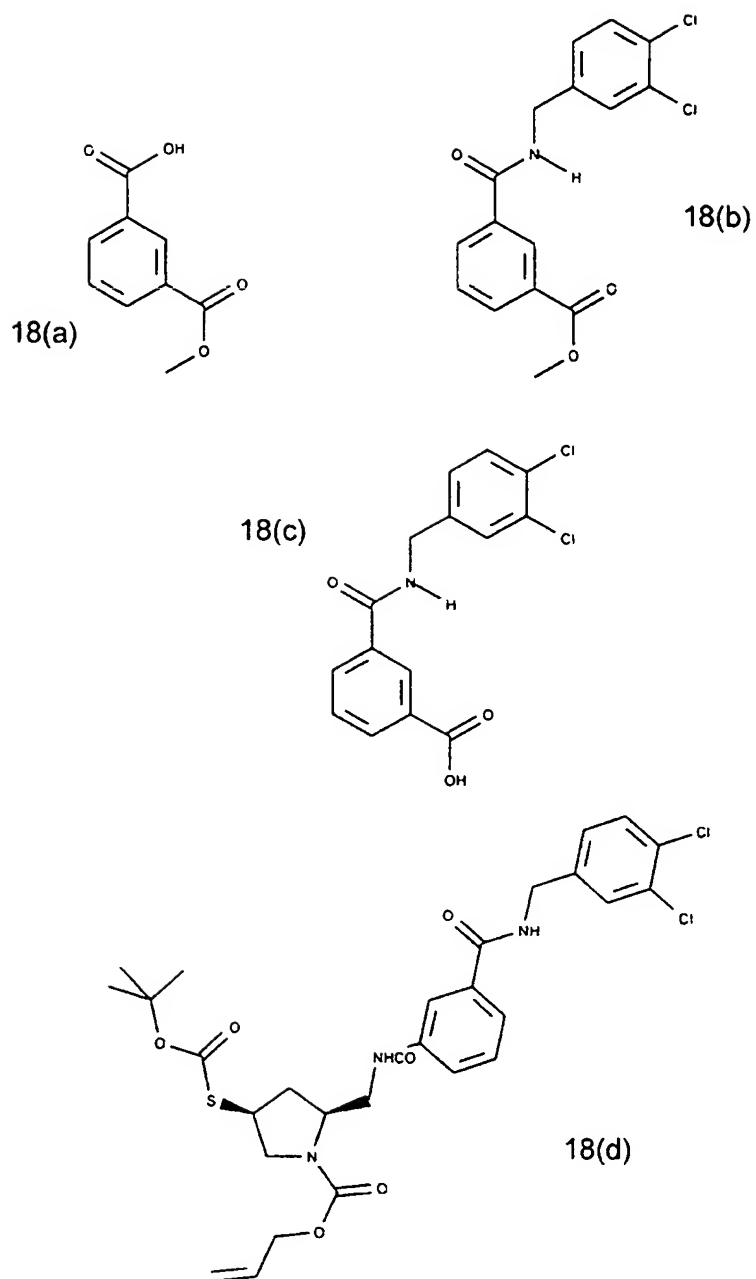
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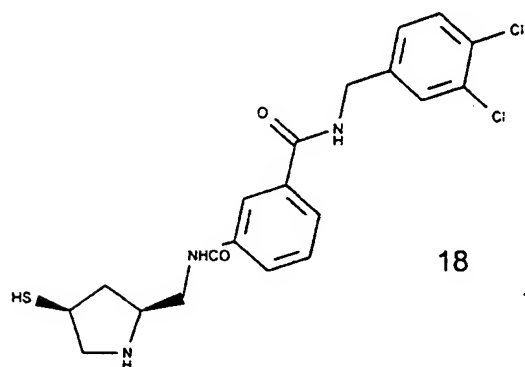
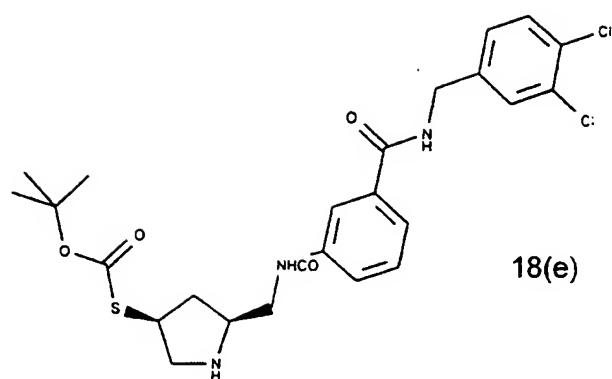


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SCHEME 18

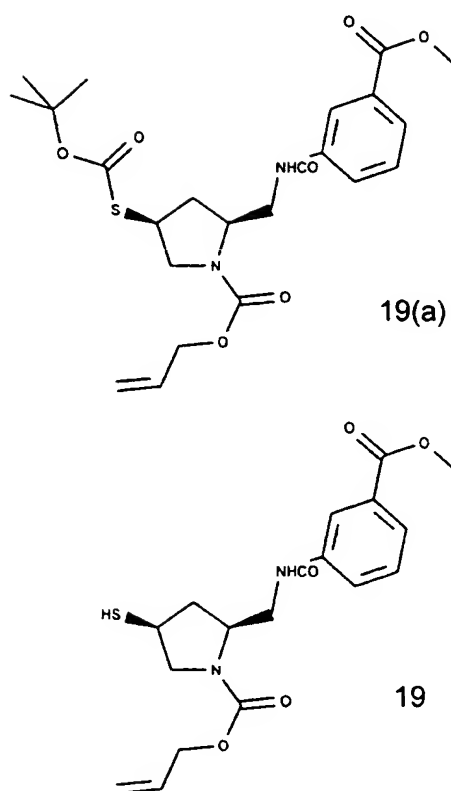


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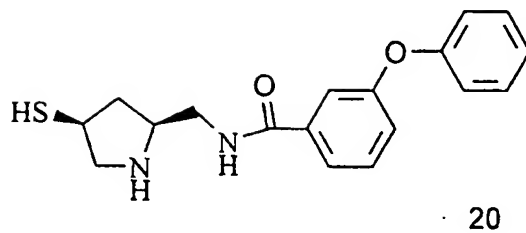
- 131 -

SCHEME 19

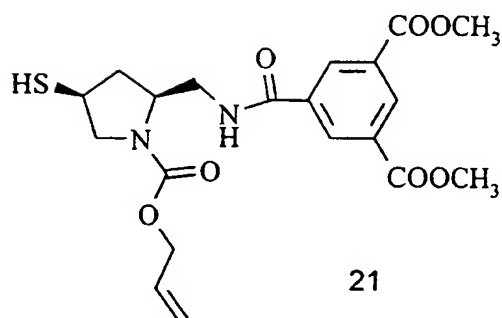


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SCHEME 20

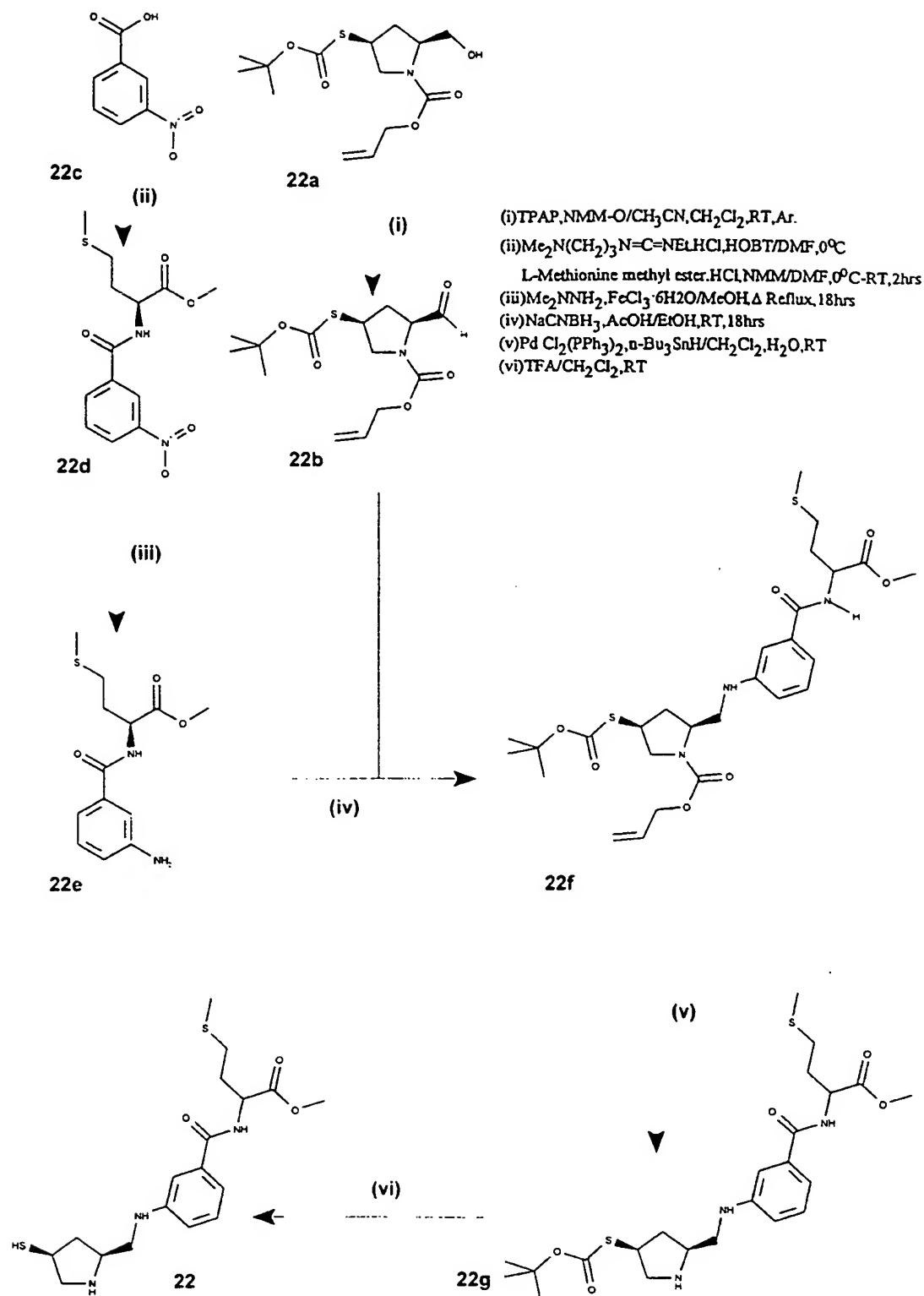


SCHEME 21



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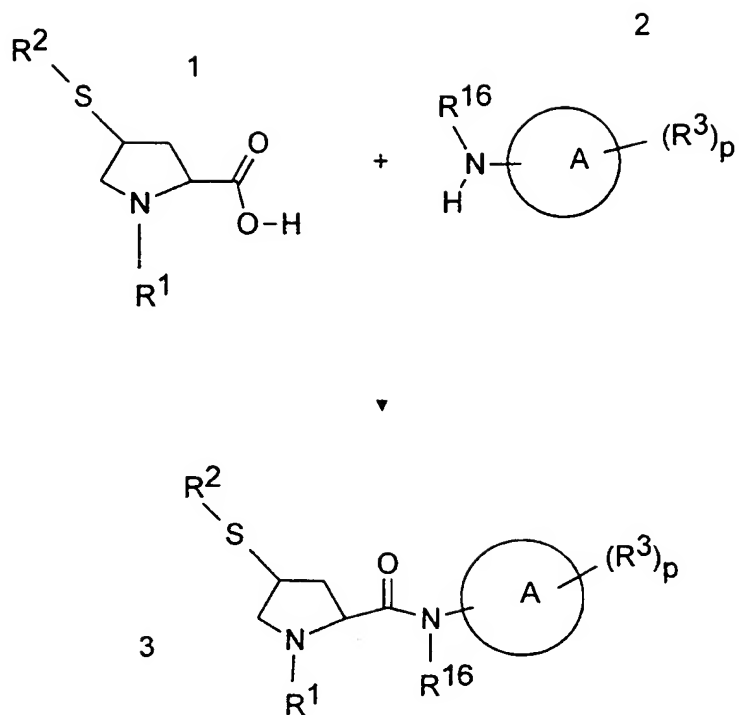
SCHEME 22



SUBSTITUTE SHEET (RULE 26)

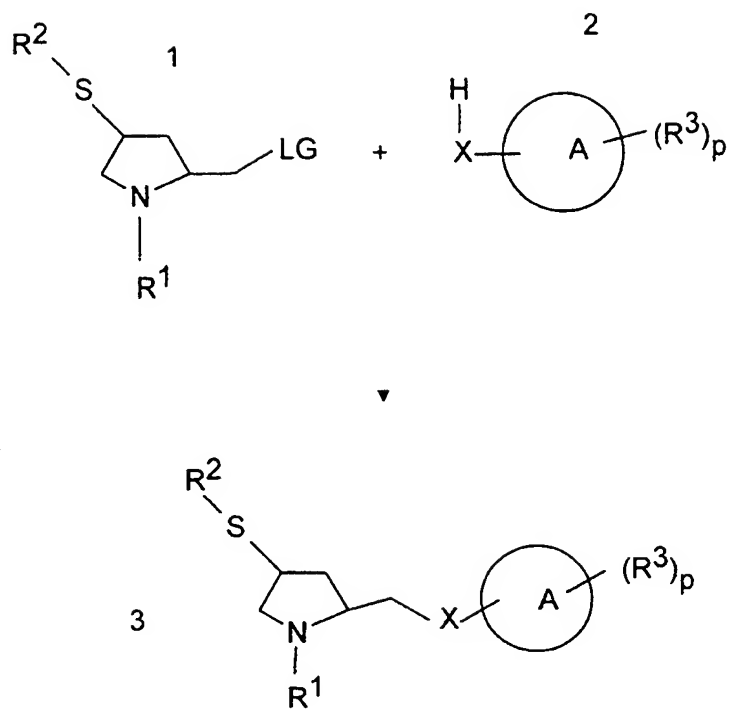
- 134 -

Scheme 23



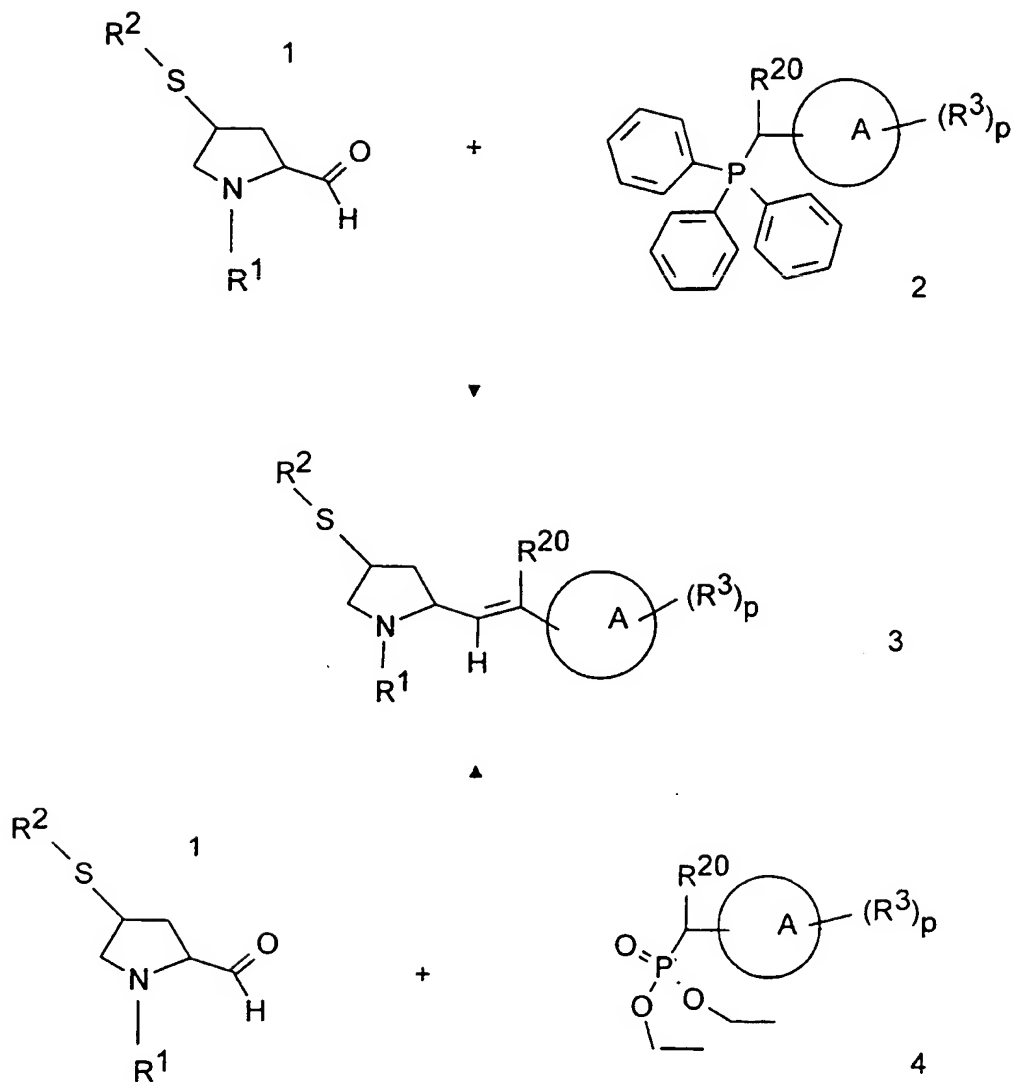
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Scheme 24



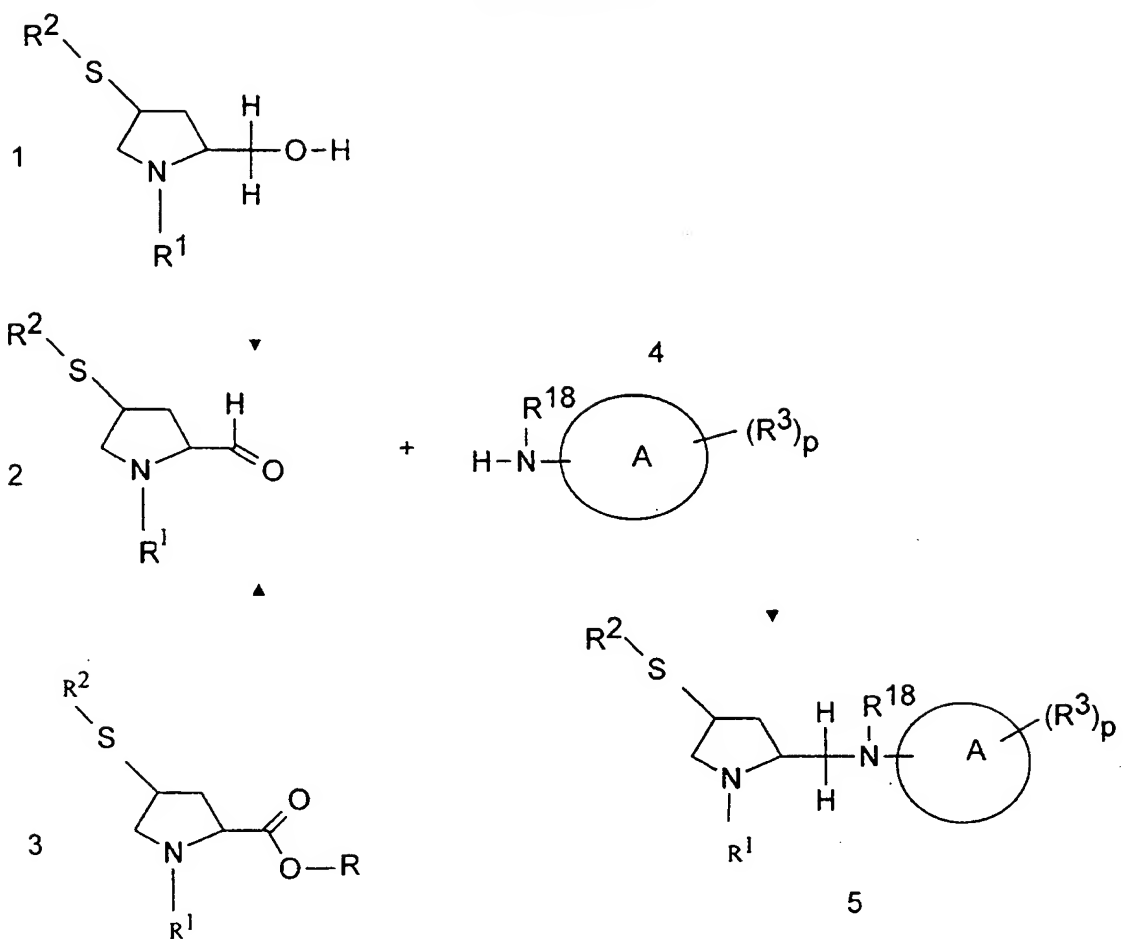
- 136 -

Scheme 25



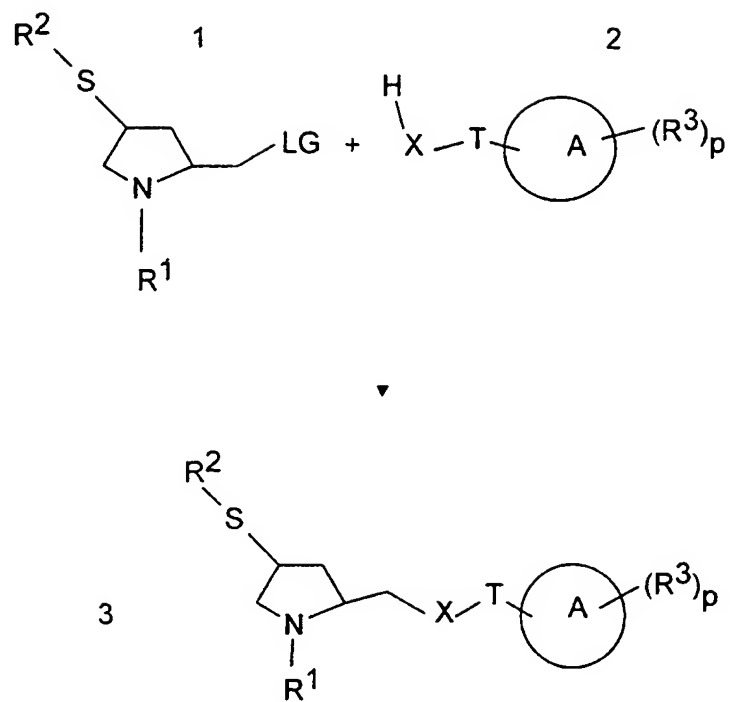
SUBSTITUTE SHEET (RULE 26)

Scheme 26

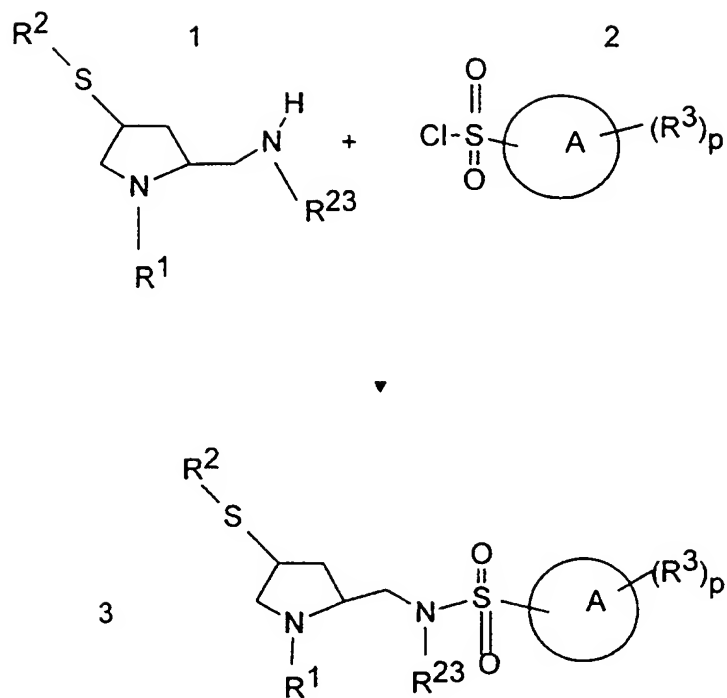


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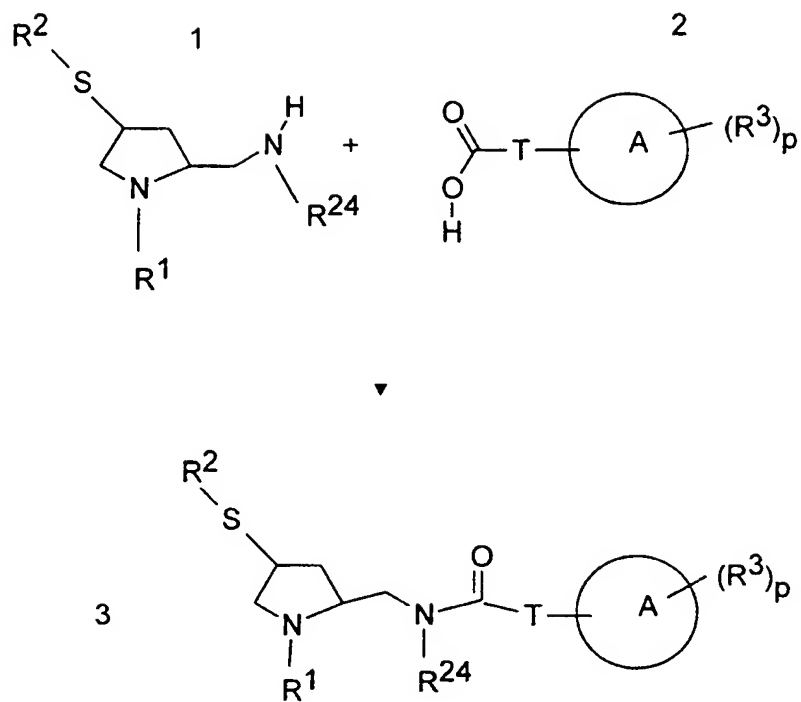
Scheme 27



Scheme 28

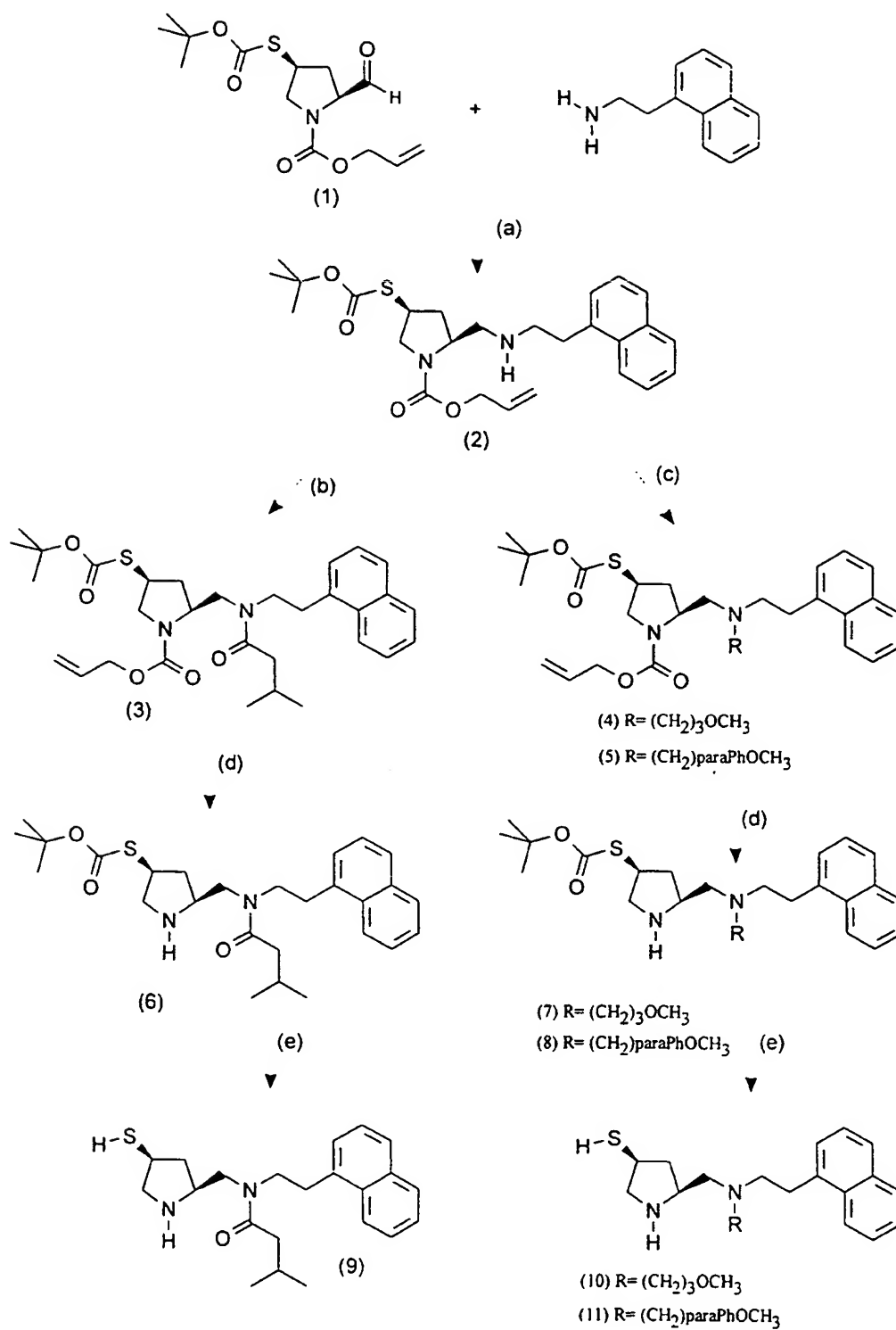


Scheme 29



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Scheme 30



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(a) 4A Molecular sieve/sodium triacetoxymethylborohydride/dichloromethane/-20deg.

(b) Isovaleryl chloride/triethylamine/dichloromethane/R.T.

(c) $R=(CH_2)_3OCH_3$, 4A Molecular sieve/sodium triacetoxymethylborohydride/dichloromethane

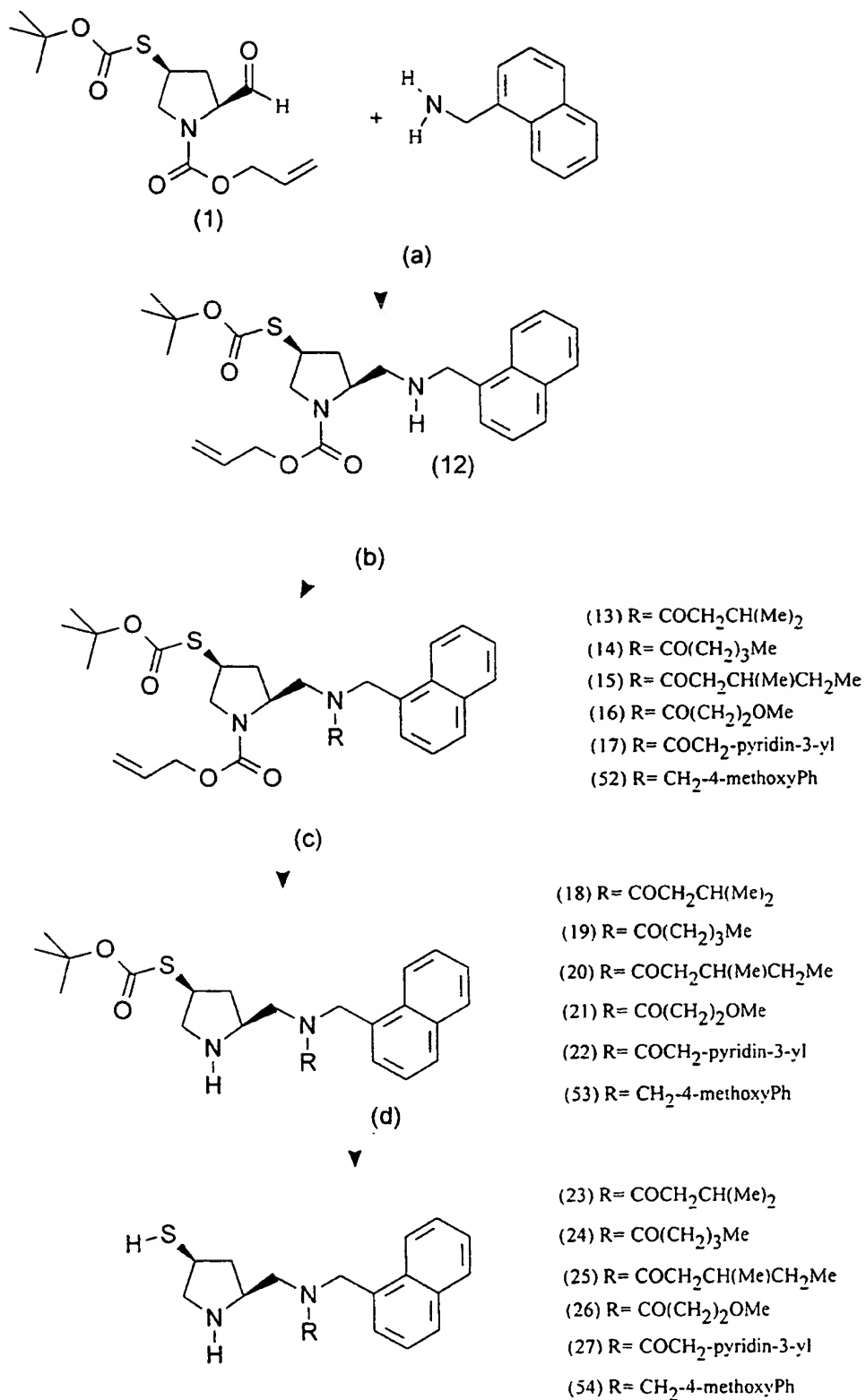
(c) $R=CH_2paraPhOCH_3$, paraMethoxybenzyl chloride/sodium bicarbonate/ H_2O /dichloromethane

(d) Tributyltin hydride/bis(triphenylphosphine)palladium(0) chloride/dichloromethane

(e) Trifluoroacetic acid/R.T..

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Scheme 31



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(a) 4A Molecular sieve/sodium triacetoxy borohydride/dichloromethane/-20deg.

(b) R=13. Isovaleryl chloride/triethylamine/dichloromethane/R.T.

R=14. Valeryl chloride/triethylamine/dichloromethane/R.T.

R=15. 3-Methylvaleric acid/EDC/

/4-Dimethylamino-pyridine/dichloromethane

R=16. 3-Methoxypropionic acid/EDC

/4-Dimethylamino-pyridine/dichloromethane

R=17. 3-Pyridylacetic acid HCl/EDC

/4-Dimethylamino-pyridine/dichloromethane

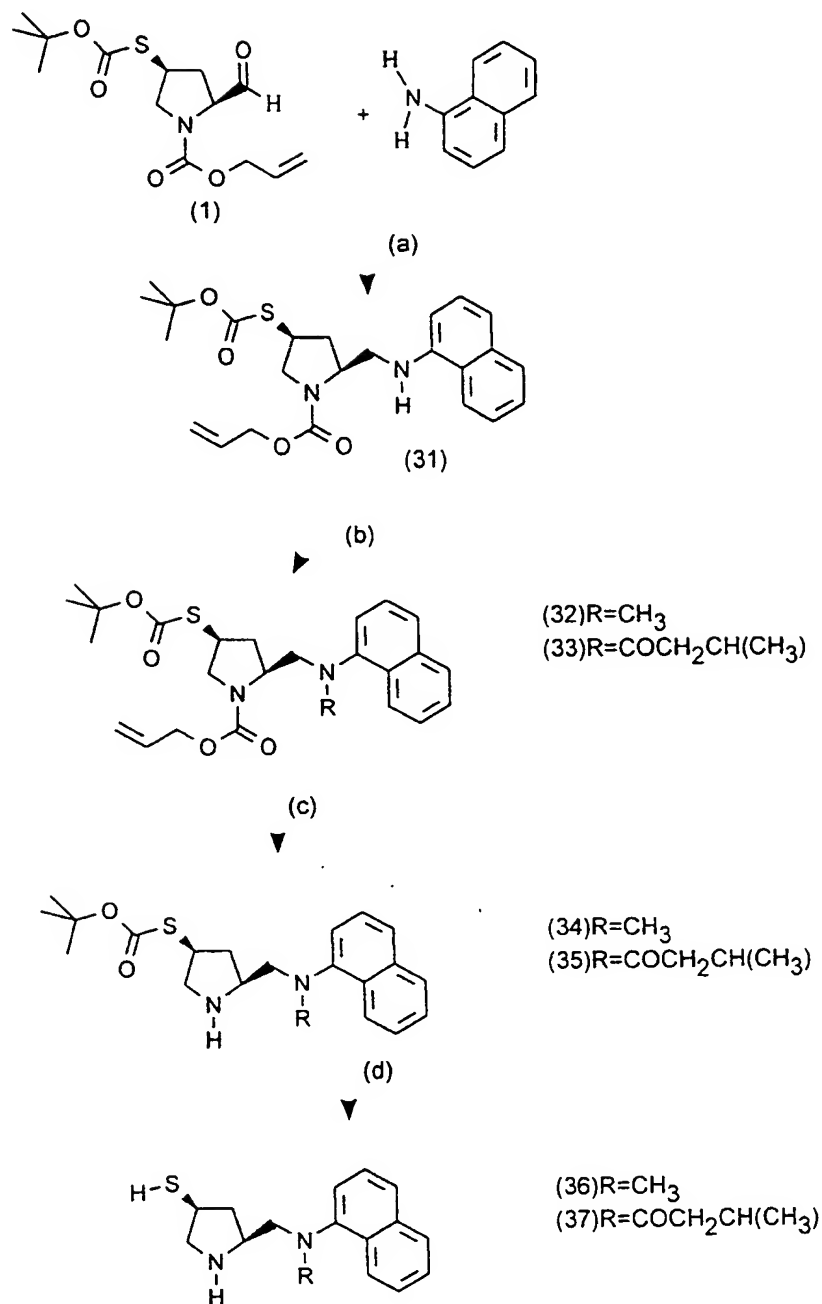
R=52. p-Methoxybenzyl chloride/potassium carbonate/DMF/70deg.

(c) Tributyltin hydride/bis(triphenylphosphine)palladium(0) chloride/dichloromethane.

(d) Trifluoroacetic acid/R.T.

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Scheme 32



(a) 3A Molecular sieve/acetic acid/ethanol/sodium cyanoboro hydride/R.T.

(b) R=CH₃, Methyl iodide/dimethyl formamide/potassium carbonate/80 deg.

R=COCH₂CH(CH₃)₂, Isovaleryl chloride/triethylamine/dichloromethane/R.T.

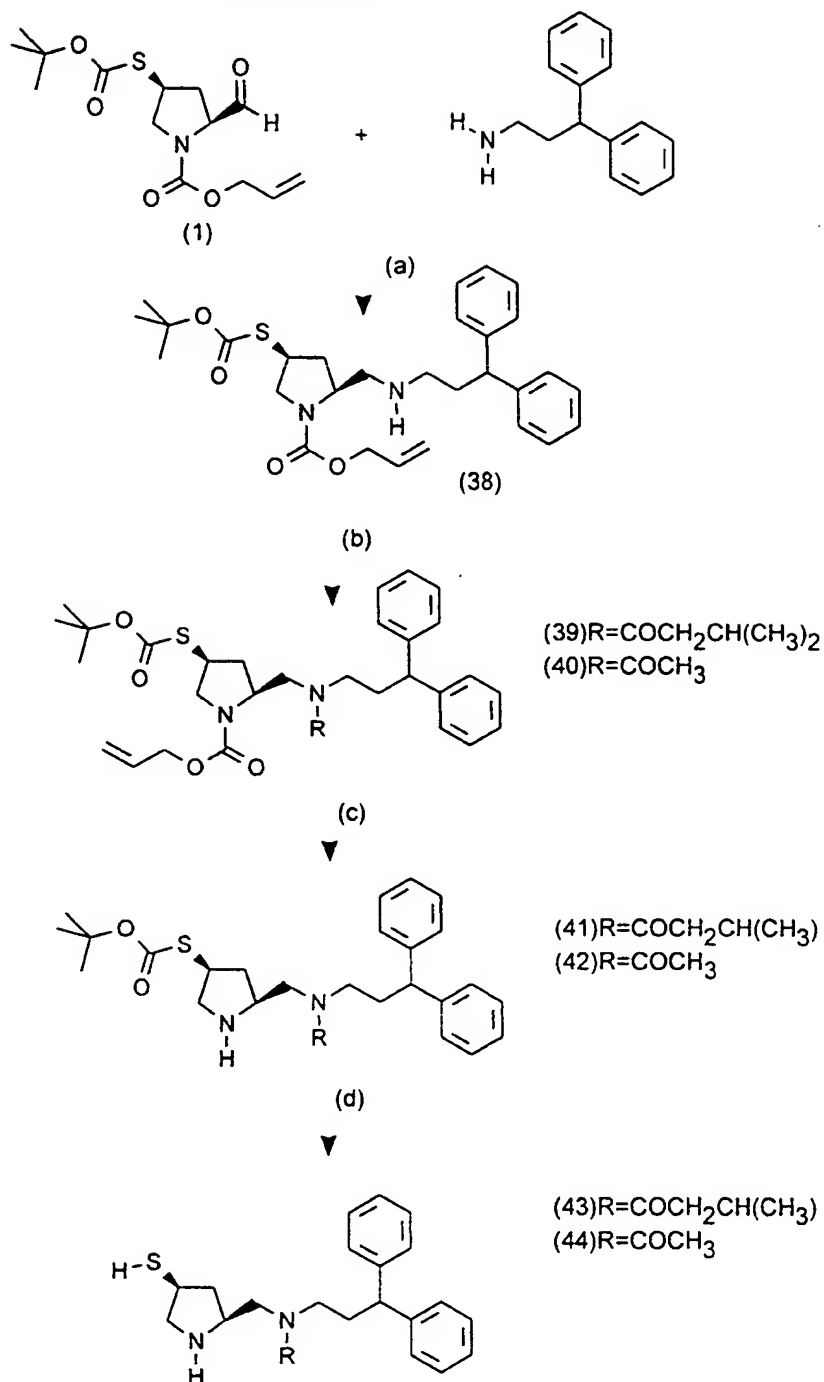
(c) Tributyltin hydride/bis(triphenylphosphine)palladium(0)chloride/dichloromethane

(d) Trifluoroacetic acid/R.T.

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Scheme 33



(a) 4A Molecular sieve/sodium triacetoxy borohydride/dichloromethane/-20deg.

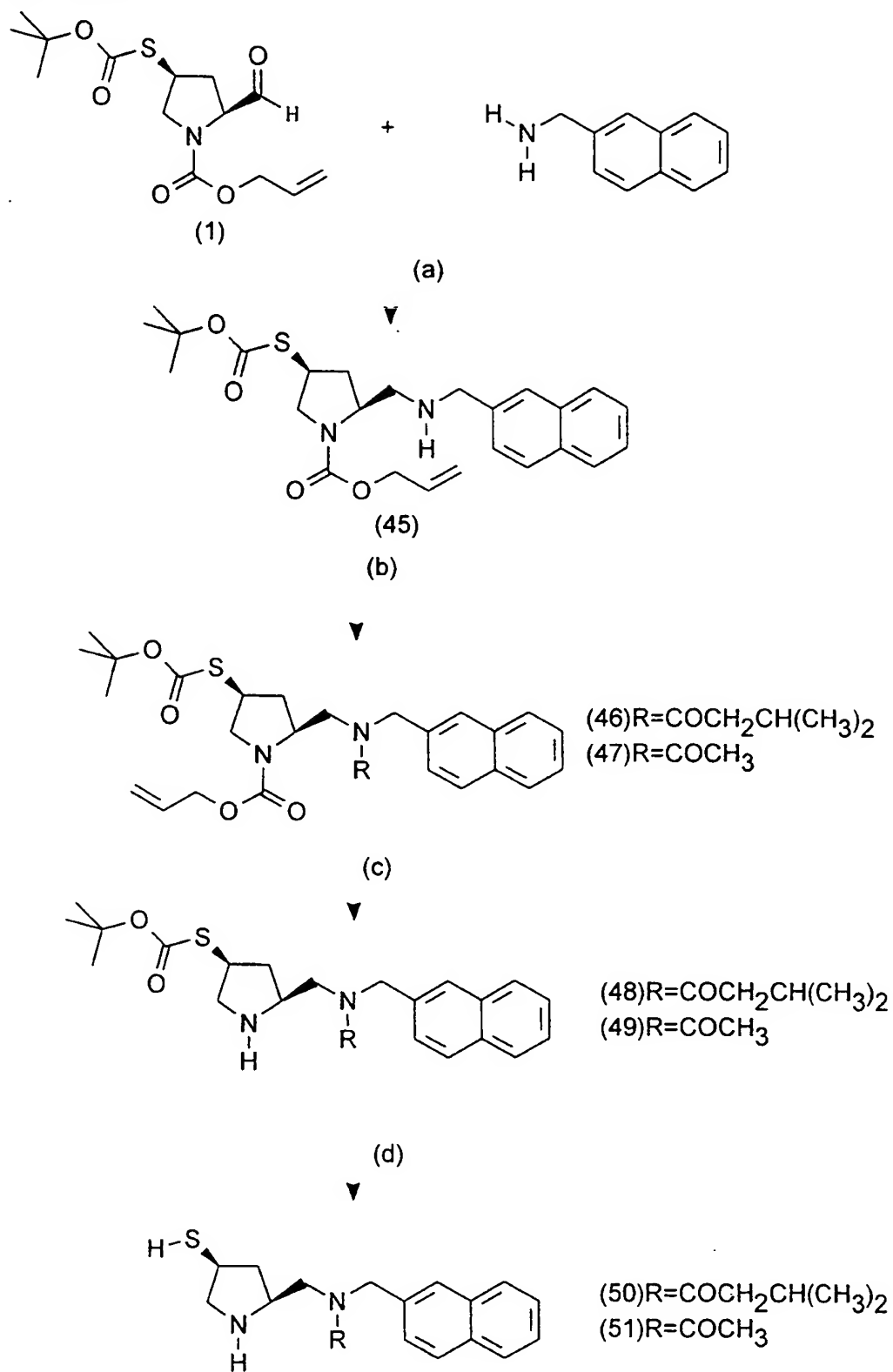
(b) $R = \text{COCH}_2\text{CH}(\text{CH}_3)_2$, Isovaleryl chloride/triethylamine/dichloromethane/R.T.
 $R = \text{COCH}_3$, Acetyl chloride/dichloromethane/triethylamine/R.T.

(c) Tributyltin hydride/bis(triphenylphosphine)palladium(0) chloride/dichloromethane

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Scheme34



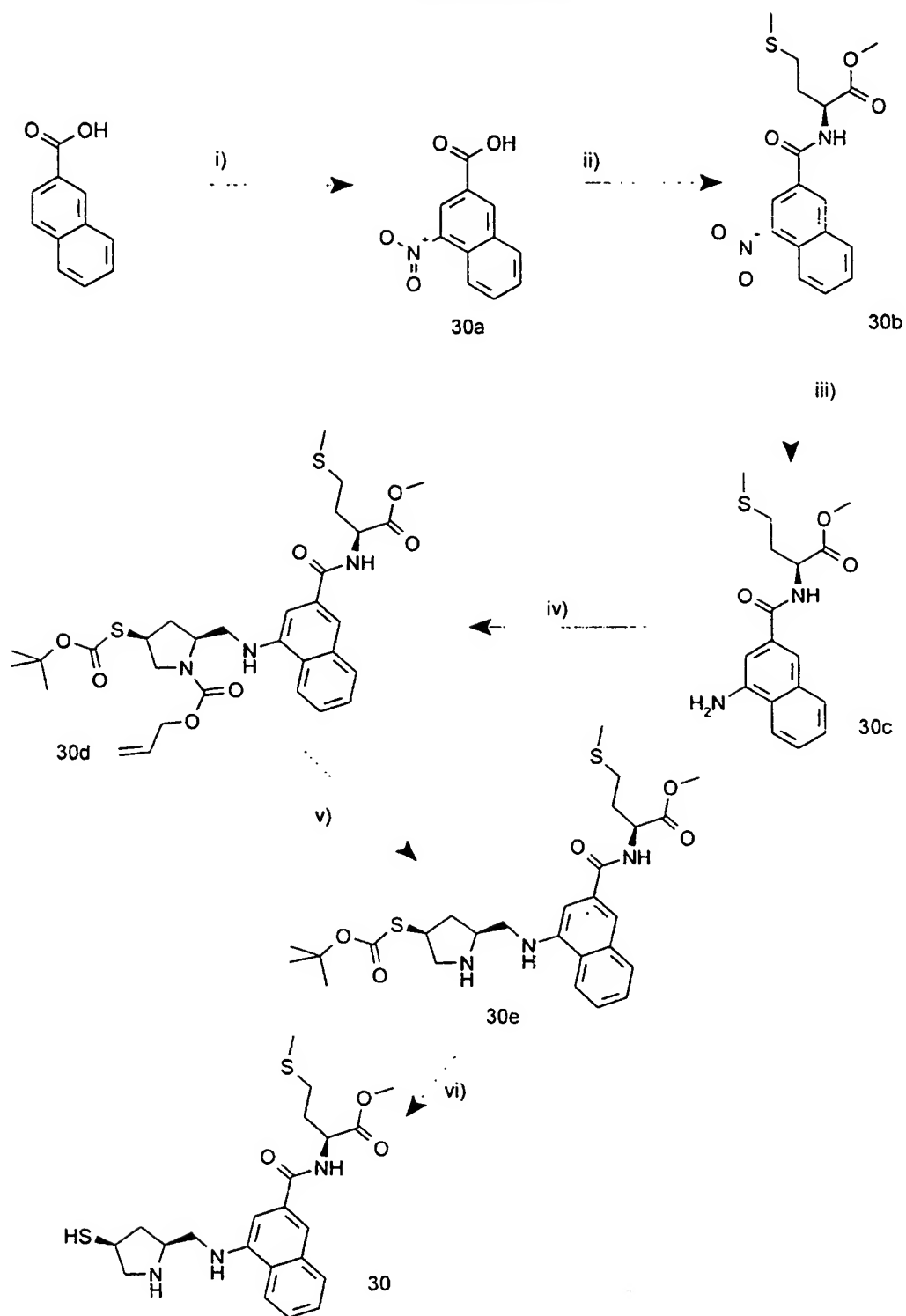
SUBSTITUTE SHEET (RULE 26)

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- (a) 4A Molecular sieve/sodium triacetoxo borohydride/dichloromethane/-20deg.
- (b) $R=COCH_2CH(CH_3)_2$, Isovaleryl chloride/triethylamine/dichloromethane/R.T.
 $R=COCH_3$, Acetyl chloride/dichloromethane/triethylamine/R.T.
- (c) Tributyltin hydride/bis(triphenylphosphine)palladium(0) chloride/dichloromethane
- (d) Trifluoroacetic acid/R.T.

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Scheme 35



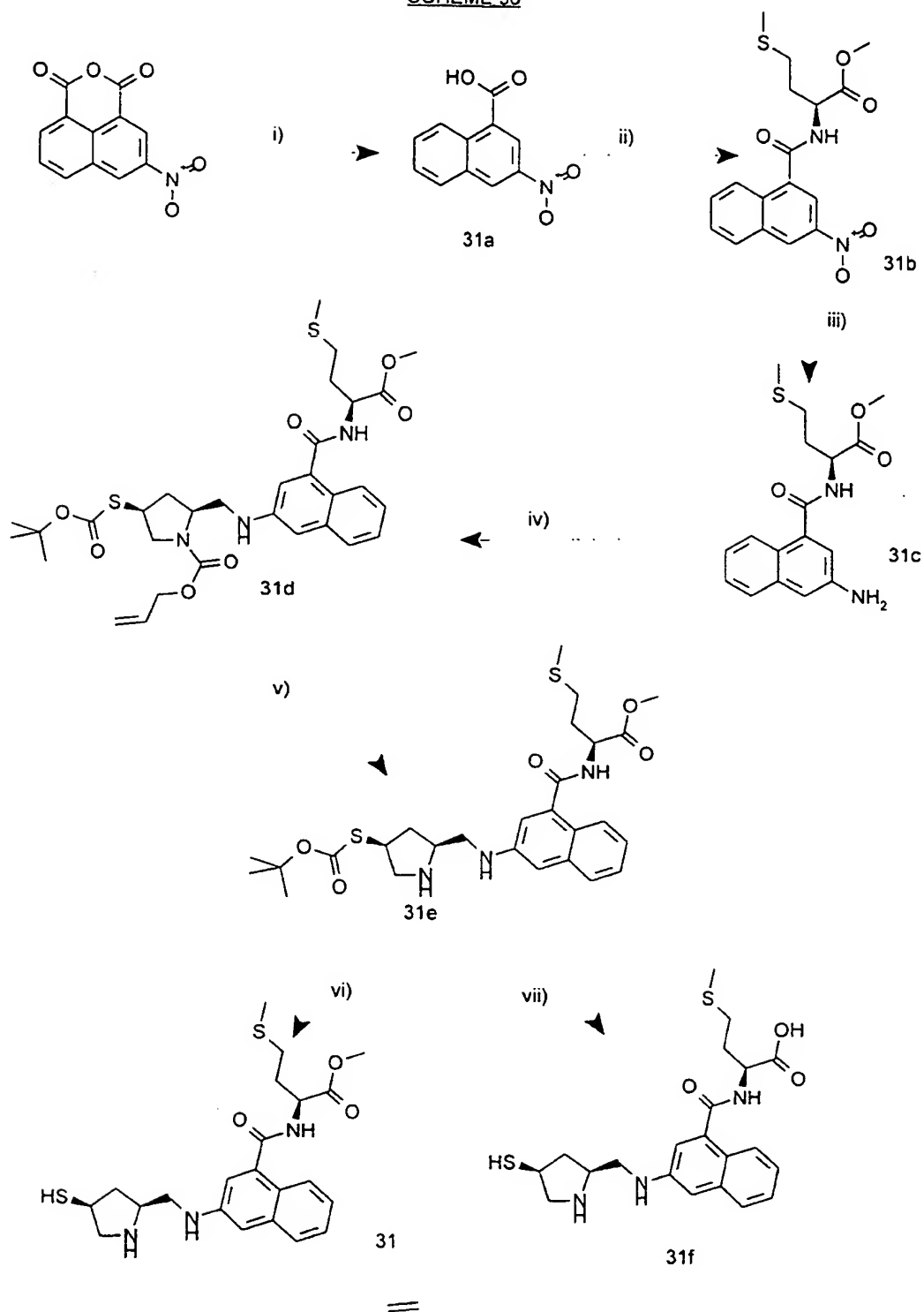
SUBSTITUTE SHEET (RULE 26)

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- i) HNO_3 , 50°C
- ii) $(\text{COCl})_2$, DMF/ CH_2Cl_2
Et₃N, L-Methionine methyl ester hydrochloride
- iii) $\text{Me}_2\text{NNH}_2 \cdot \text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ /MeOH Δ Reflux
- iv) **22b**/MeOH, 3A° sieves
AcOH, NaCNBH₃
- v) $\text{PdCl}_2(\text{PPh}_3)_2$, ⁿBu₃SnH/ CH_2Cl_2 , H₂O
- vi) TFA

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SCHEME 36



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i) G.J. Leuck et al JACS 51, 1831.1929

ii) EDC.HOBT/DMF 0°C

NMM.L-Methionine methyl ester hydrochloride 0°C-RT

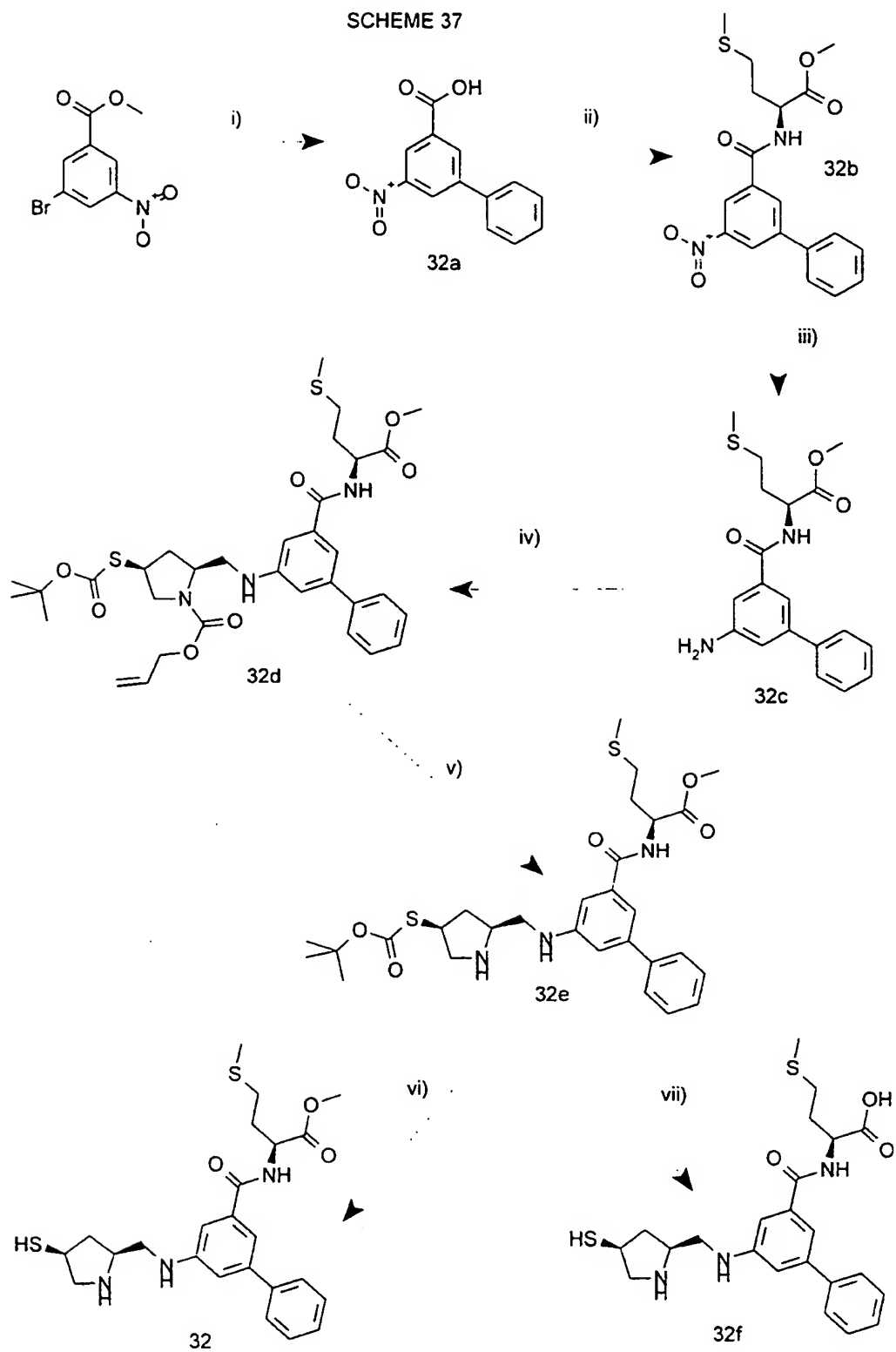
iii) Me₂NNH₂.FeCl₃.6H₂O/MeOH Δ Refluxiv) **22b**/MeOH, 3A° sievesAcOH.NaCNBH₃v) PdCl₂(PPh₃)₂, ⁿBu₃SnH/CH₂Cl₂.H₂O

vi) TFA

vii) 2N NaOH/MeOH

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SCHEME 37



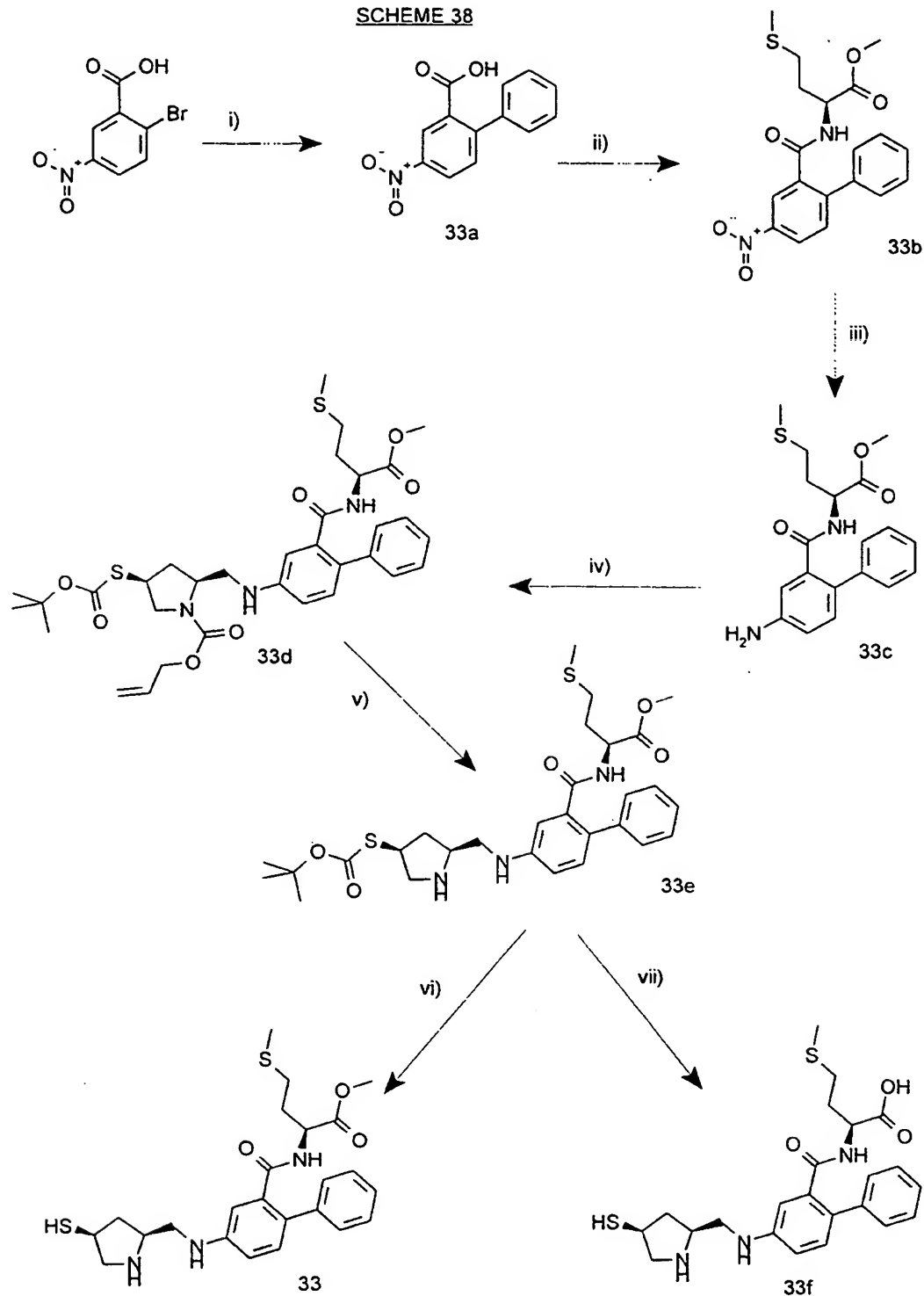
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- i) PhB(OH)_2 , $(\text{PPh}_3)_4 \text{Pd}^0$ /DME. NaHCO_3 (aq) Δ Reflux
- ii) EDC, HOBT/DMF 0°C
NMM.L-Methionine methyl ester hydrochloride 0°C -RT
- iii) Me_2NNH_2 , $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ /MeOH Δ Reflux
- iv) **22b**/MeOH, 3A° sieves
AcOH. NaCNBH_3
- v) $\text{PdCl}_2(\text{PPh}_3)_2$, $^t\text{Bu}_3\text{SnH}$ / CH_2Cl_2 , H_2O
- vi) TFA
- vii) 2N NaOH/MeOH

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SCHEME 38

i) PhB(OH)_2 , $(\text{PPh}_3)_4 \text{Pd}^0$ /DME, $\text{NaHCO}_3(\text{aq})$ Δ Refluxii) EDC, HOBT/DMF 0°C NMM, L-Methionine methyl ester hydrochloride 0°C -RTiii) Me_2NNH_2 , $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ /MeOH Δ Refluxiv) 22b/MeOH, 3A° sieves

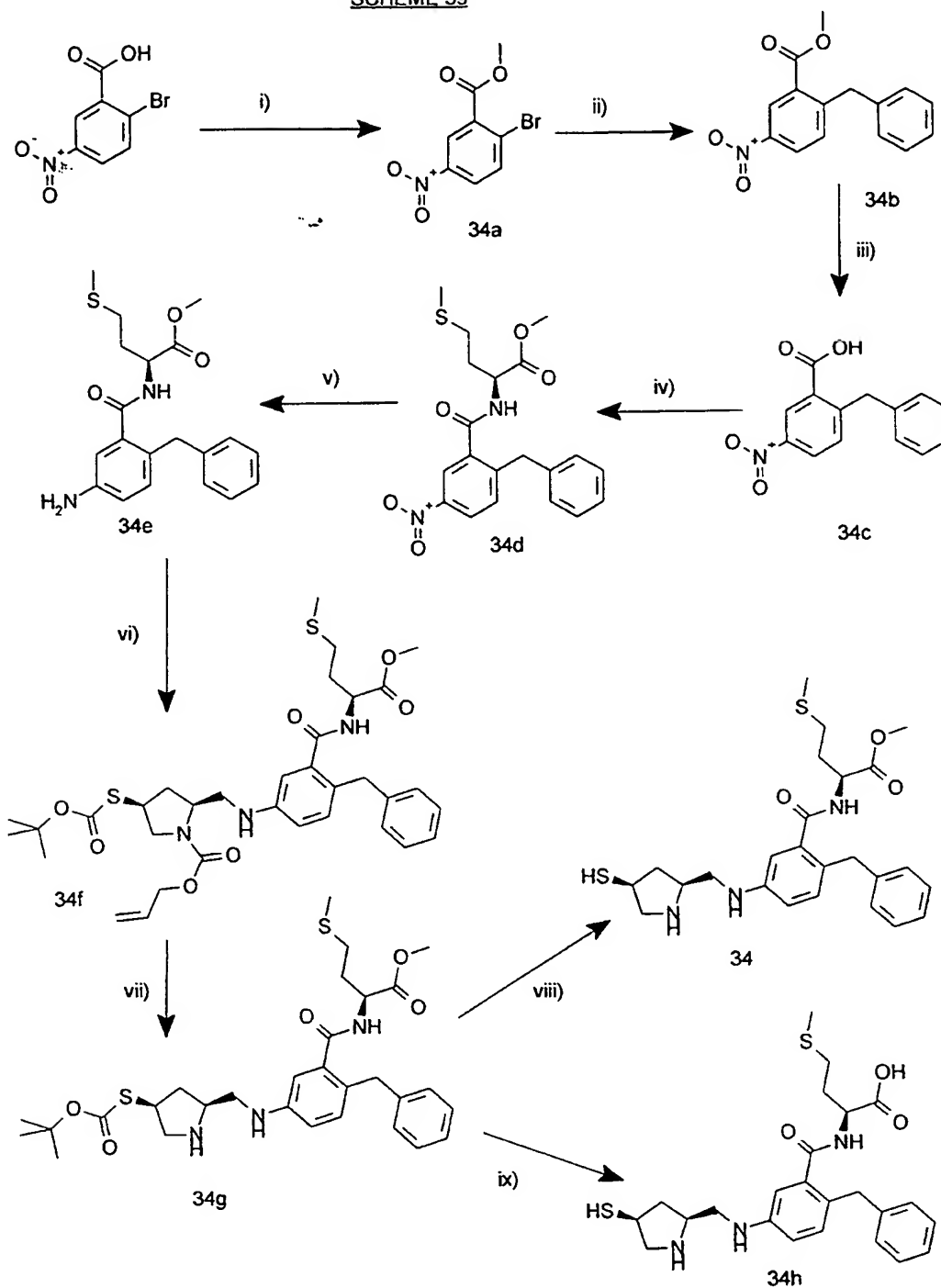
SUBSTITUTE SHEET (RULE 26)

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AcOH, NaCNBH₃
v) PdCl₂(PPh₃)₂, ⁿBu₃SnH/CH₂Cl₂.H₂O
vi) TFA
vii) 2N NaOH/MeOH

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SCHEME 39



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vi) 22b/MeOH.3A° sieves

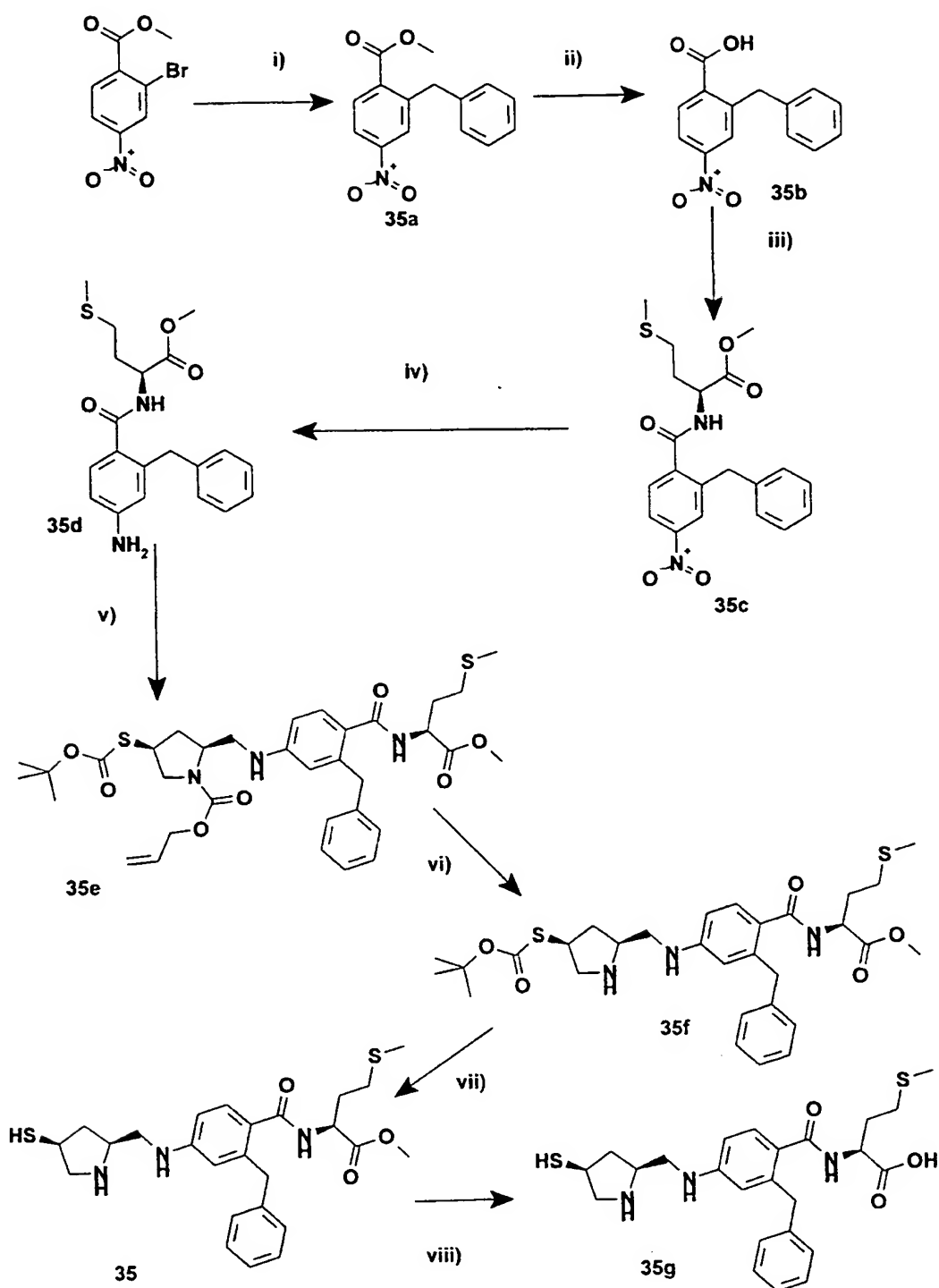
AcOH.NaCNBH₃vii) PdCl₂(PPh₃)₂, ⁿBu₃SnH/CH₂Cl₂, H₂O

viii) TFA

ix) 2N NaOH/MeOH

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SCHEME 40



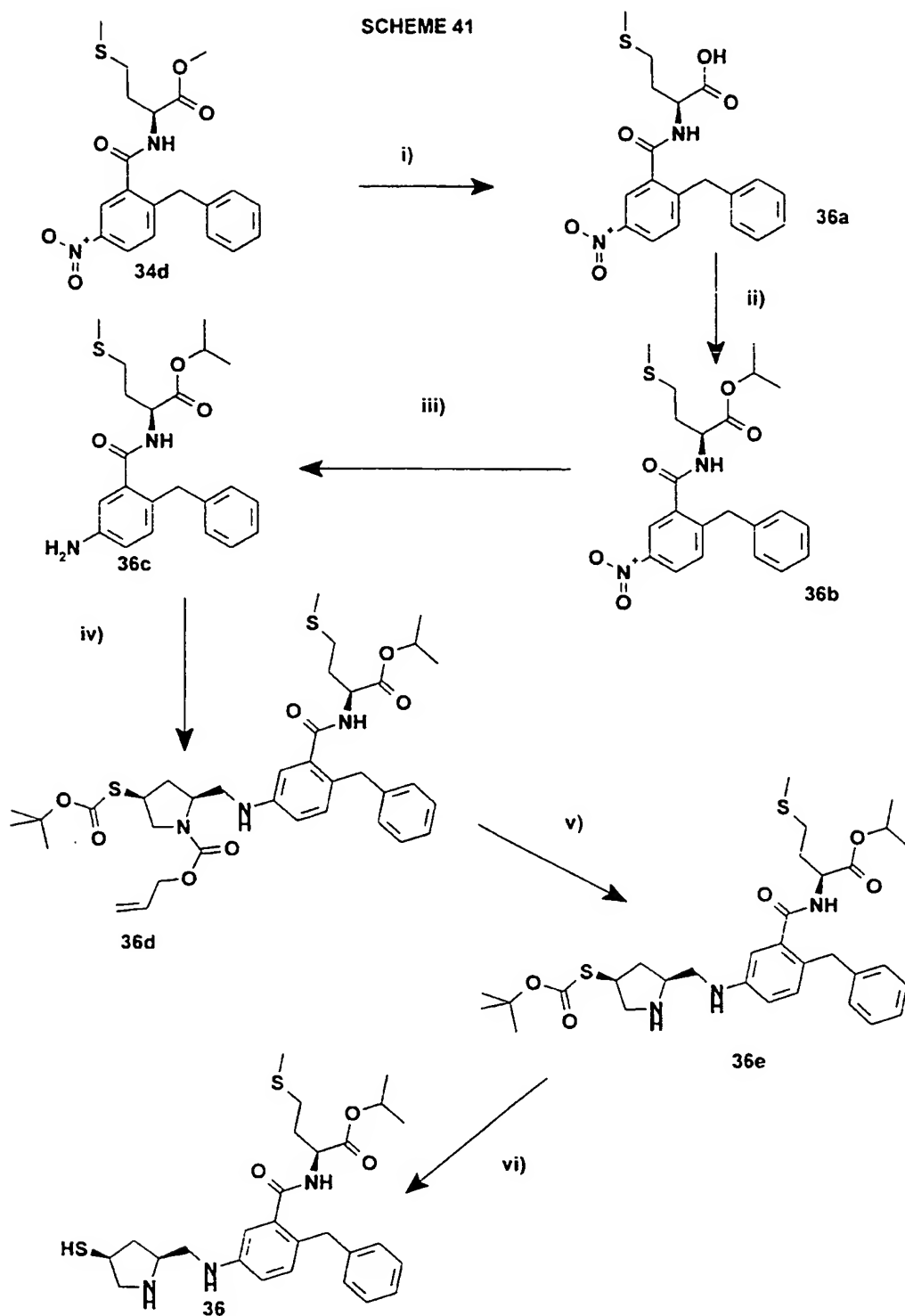
i) BzZnBr , $\text{Pd}_2(\text{dba})_3$ / THF
 ii) 2N NaOH/MeOH
 iii) EDC, HOBT/DMF 0°C

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- NMM.L-Methionine methyl ester hydrochloride 0°C-RT
- iv) $\text{SnCl}_2 \cdot 2\text{H}_2\text{O} / \text{EtOAc}$ Δ Reflux
 - v) **22b**/MeOH, 3A^o sieves
AcOH.NaCNBH₃
 - vi) $\text{PdCl}_2(\text{PPh}_3)_2$, ⁿBu₃SnH/CH₂Cl₂.H₂O
 - vii) TFA
 - viii) 2N NaOH/MeOH

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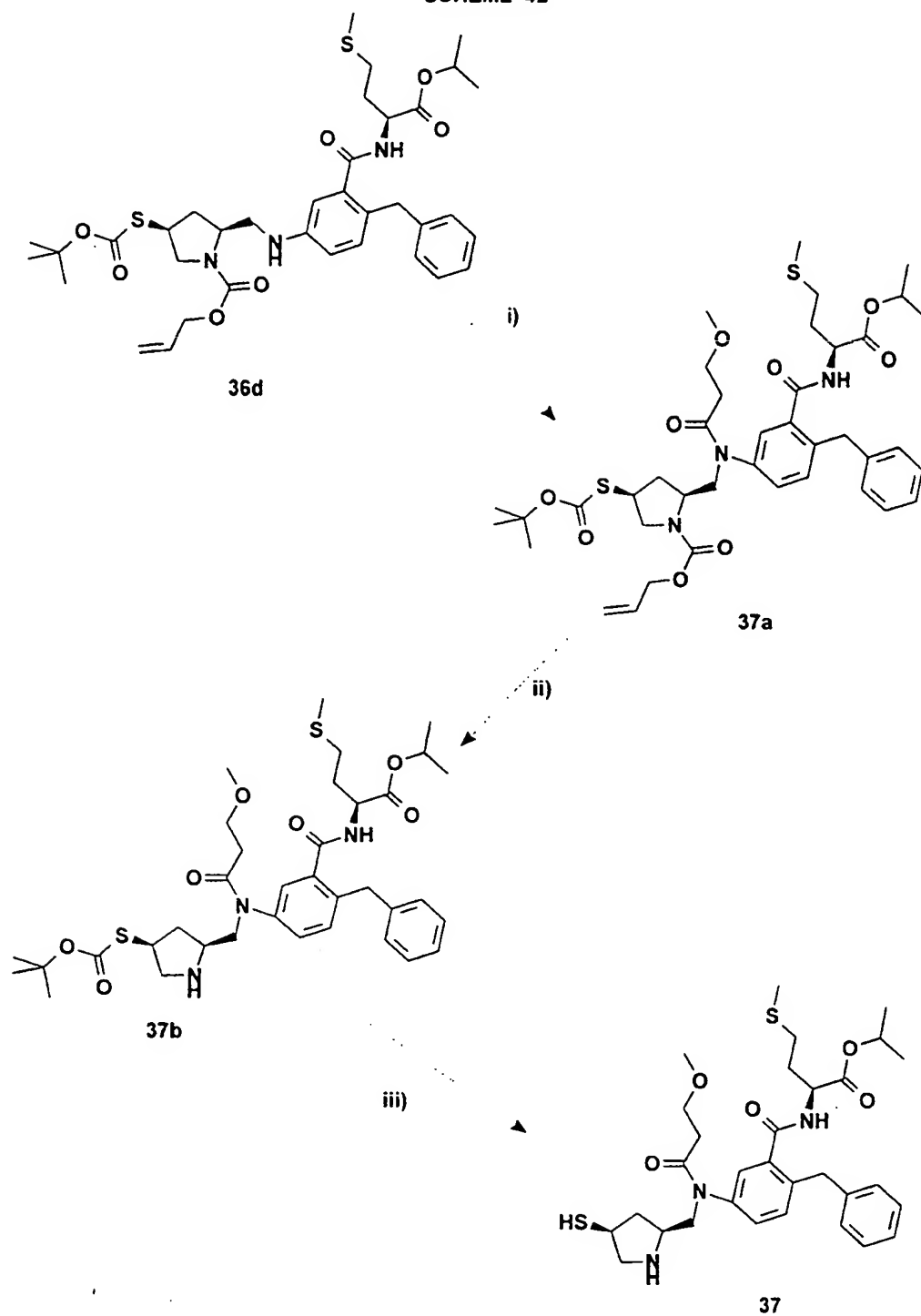
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- i) 2N NaOH/MeOH
- ii) SO_2Cl_2 /IPA Δ Reflux
- iii) $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ /EtOAc Δ Reflux
- iv) **22b**/IPA.3A^o sieves
AcOH.NaCNBH₃
- v) $\text{PdCl}_2(\text{PPh}_3)_2$, ⁿBu₃SnH/ CH_2Cl_2 .H₂O
- vi) TFA

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SCHEME 42

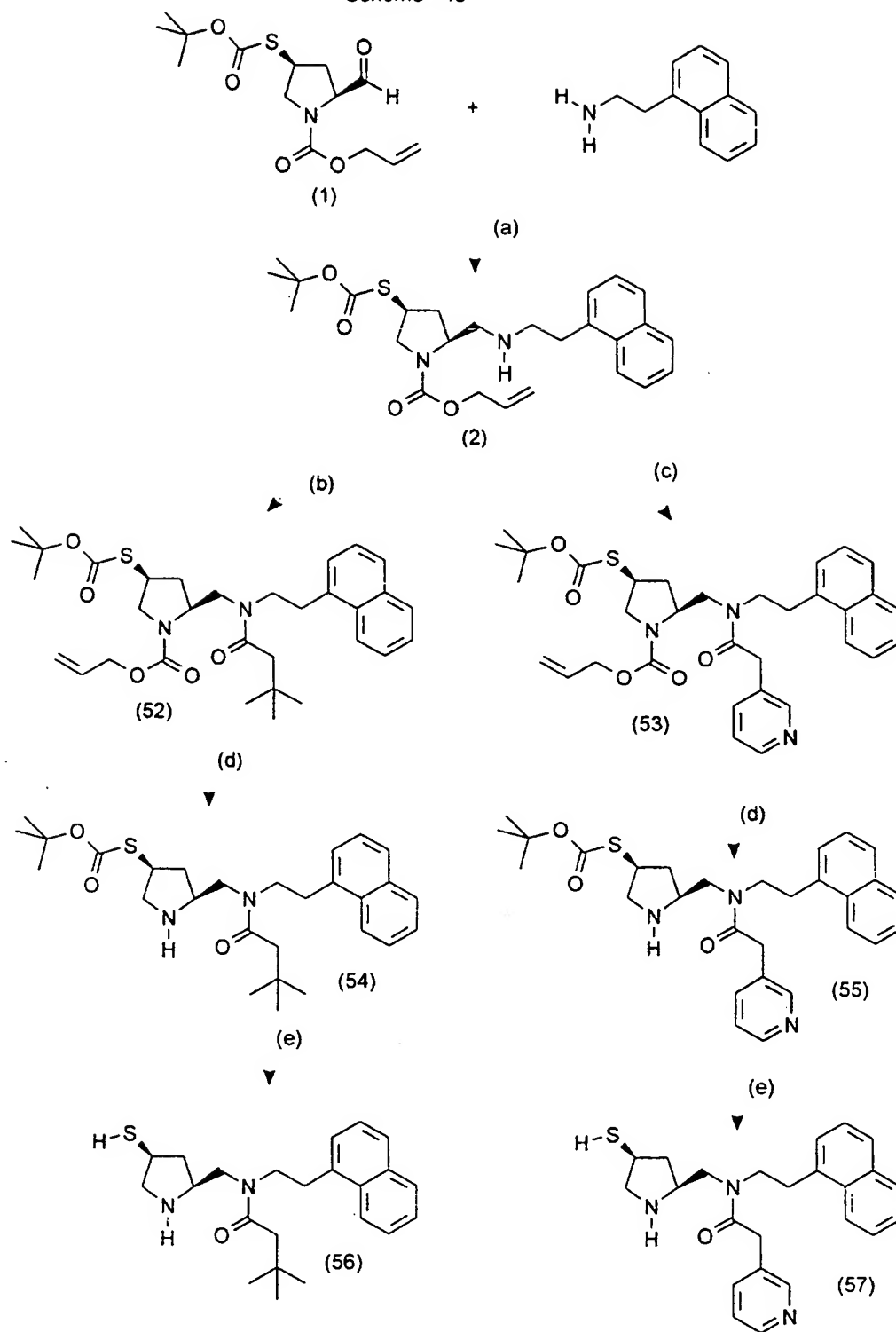


- i) $\text{CH}_3\text{O}(\text{CH}_2)_2\text{CO}_2\text{H}$, EEDQ/ CH_2Cl_2
 ii) $\text{PdCl}_2(\text{PPh}_3)_2$, $n\text{Bu}_3\text{SnH}$ / CH_2Cl_2 , H_2O
 iii) TFA

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Scheme 43



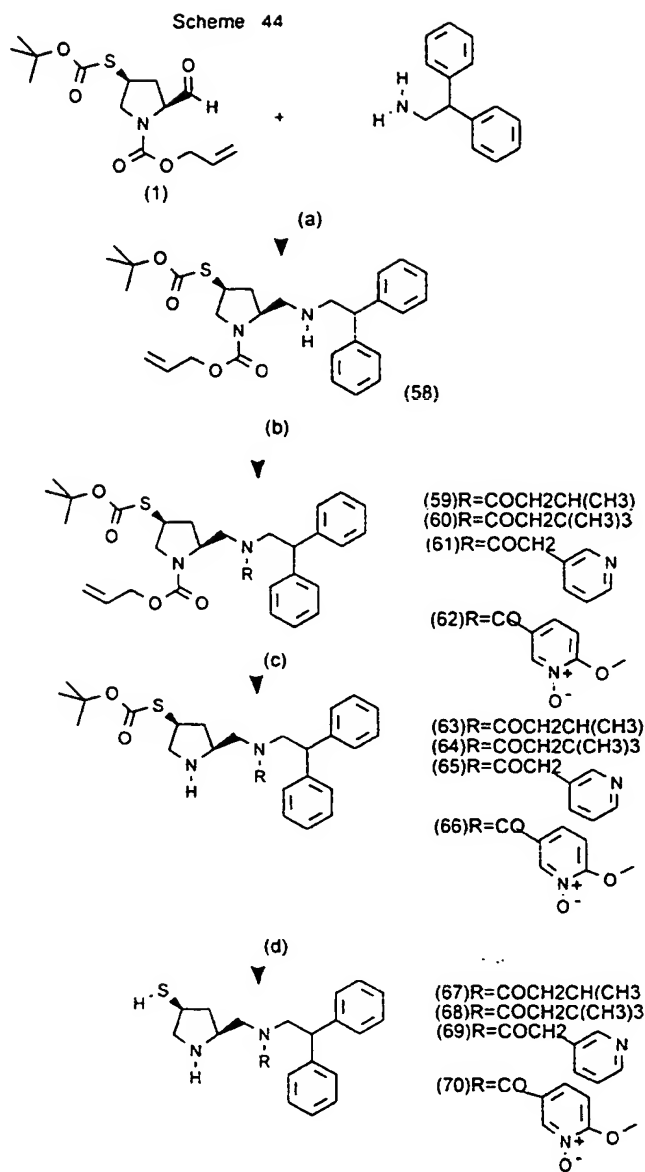
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Scheme 43(cont.)

- (a) 4A Molecular sieve/sodium triacetoxy borohydride/dichloromethane/-20deg.
- (b) Tert.butylacetyl chloridel/triethylamine/dichloromethane/R.T.
- (c) 3-Pyridylacetic acid/EDC/HOBT/N-methylmorpholine/dichloromethane/0deg-R.T.
- (d) Tributyltin hydride/bis(triphenylphosphine)palladium(0) chloride/dichloromethane
- (e) Trifluoroacetic acid/R.T.

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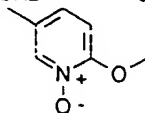


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Scheme 44(cont.)

(a) 4A Molecular sieve/sodium triacetoxy borohydride/dichloromethane/-20deg.

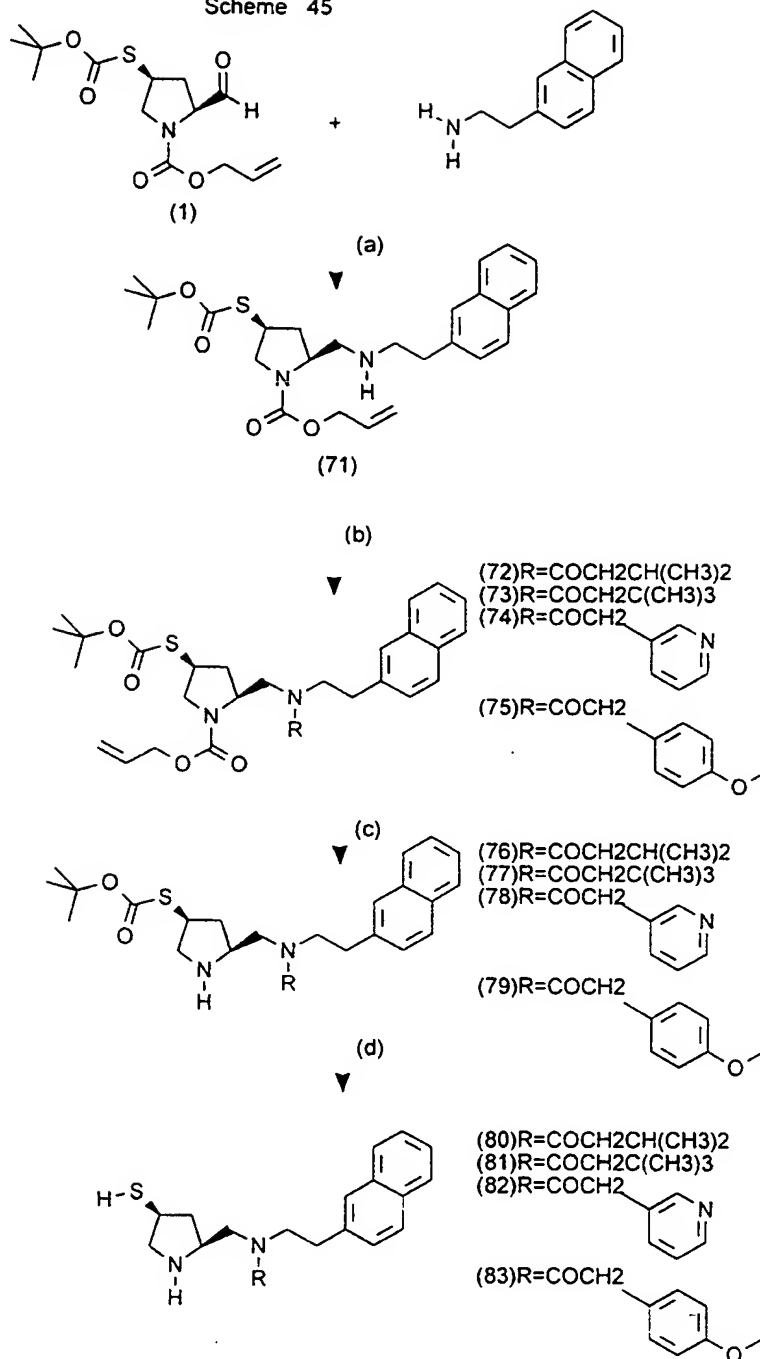
(b) R=COCH₂CH(CH₃)₂, Isovaleryl chloride/triethylamine/dichloromethane/R.T.R=COCH₂C(CH₃)₃, Tert. butylacetyl chloride/dichloromethane/triethylamine/R.T.R=COCH₂ 3-Pyridylacetic acid/EDC/HOBT/N-methylmorpholine/dichloromethane.R=COCH₂6-Methoxy-1-oxo-nicotinic acid/EDC/HOBT/N-methylmorpholine/
dichloromethane.

(c) Tributyltin hydride/bis(triphenylphosphine)palladium(0) chloride/dichloromethane

(d) Trifluoroacetic acid/R.T.

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Scheme 45




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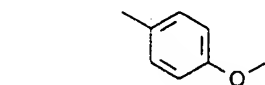
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Scheme 45(cont.)

(a) 4A Molecular sieve/sodium triacetoxy borohydride/dichloromethane/-20deg.

(b) $R=COCH_2CH(CH_3)_2$, Isovaleryl chloride/triethylamine/dichloromethane/R.T. $R=COCH_2C(CH_3)_3$, Tert.butylacetyl chloride/dichloromethane/triethylamine/R.T. $R=COCH_2$ 3-Pyridylacetic acid/EDC/HOBT/N-methylmorpholine/dichloromethane.


$R=COCH_2$ 4-Methoxyphenylacetic acid/EDC/HOBT/N-methylmorpholine/dichloromethane.

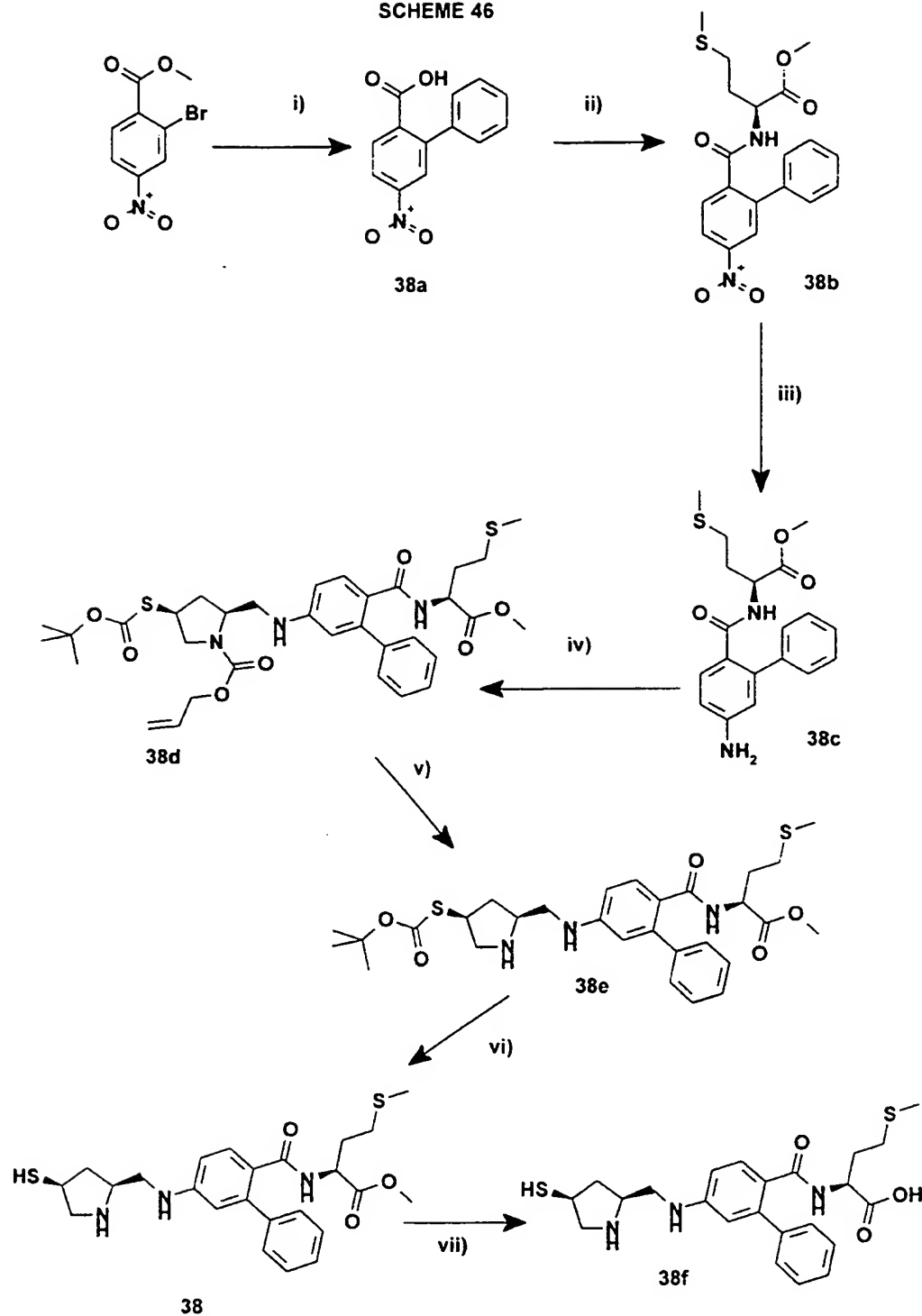


(c) Tributyltin hydride/bis(triphenylphosphine)palladium(0) chloride/dichloromethane

(d) Trifluoroacetic acid/R.T.

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SCHEME 46



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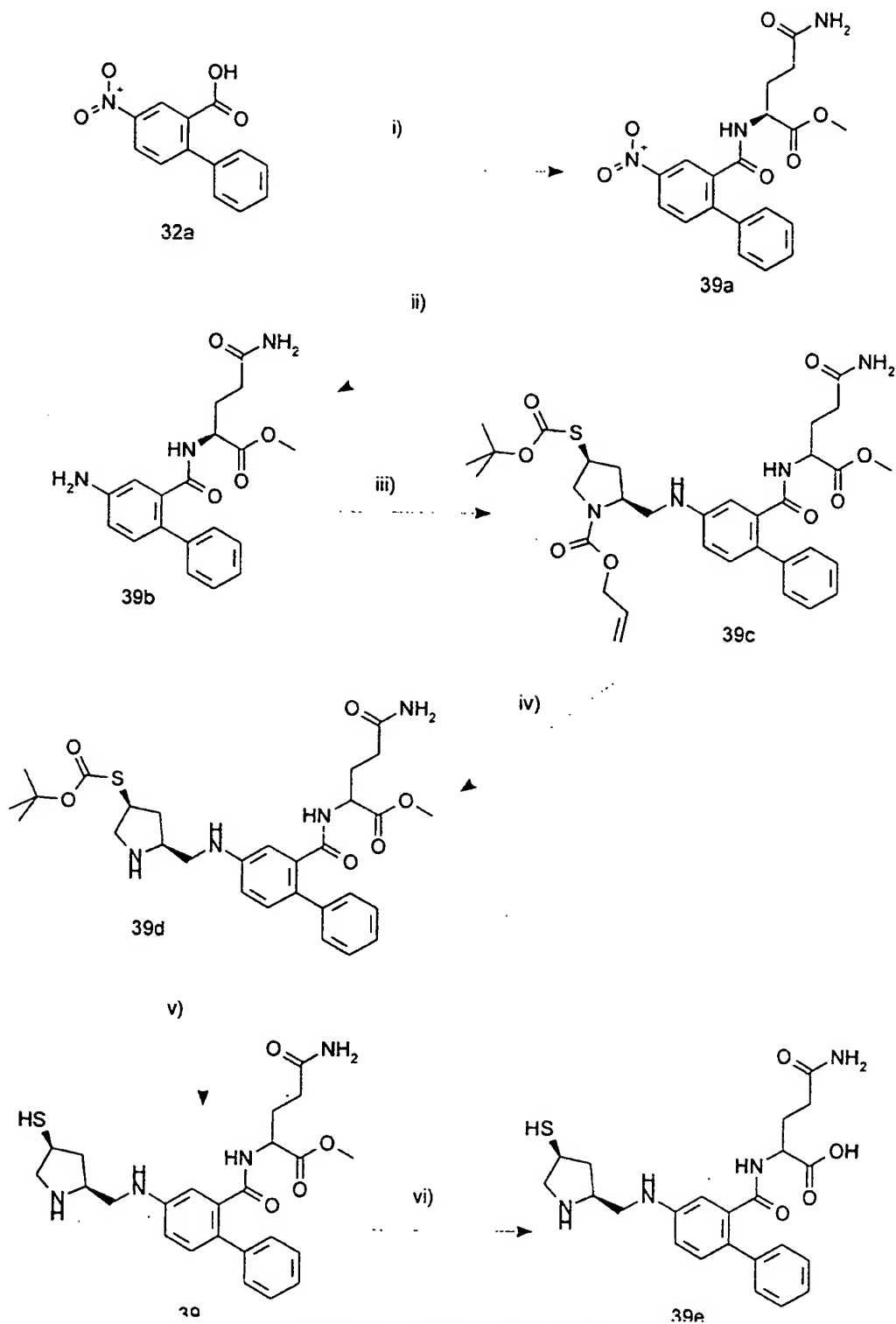
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SCHEME 46 (contd.)

- i) PhB(OH)_2 , $(\text{PPh}_3)_4 \text{Pd}^0$ /DME. NaHCO_3 (aq) Δ Reflux
- ii) EDC.HOBT/DMF 0°C
NMM.L-Methionine methyl ester hydrochloride 0°C -RT
- iii) $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ /EtOAc Δ Reflux
- iv) **22b**/MeOH.3A $^\circ$ sieves
AcOH. NaCNBH_3
- v) $\text{PdCl}_2(\text{PPh}_3)_2$, $^n\text{Bu}_3\text{SnH}$ / CH_2Cl_2 , H_2O
- vi) TFA
- vii) 2N NaOH/MeOH

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SCHEME 47



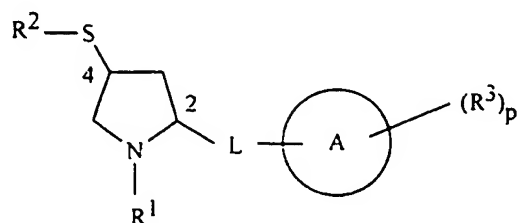
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- i) EDC.HOBT/DMF 0°C
NMM.L-Glutamine methyl ester hydrochloride 0°C-RT
- ii) $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ /EtOAc Δ Reflux
- iii) **22b**/MeOH, 3A° sieves
AcOH, NaCNBH₃
- iv) $\text{PdCl}_2(\text{PPh}_3)_2$, ⁿBu₃SnH/CH₂Cl₂, H₂O
- v) TFA
- vi) 2N NaOH/MeOH

CLAIMS

1. A pharmaceutical composition comprising an inhibitor of ras farnesylation of Formula I



Formula I

wherein:

- R^1 is selected from H; $-C_{1-4}$ alkyl; $-C_{1-3}$ alkylene-Ph optionally mono or di-substituted on Ph with substituents selected from C_{1-4} alkyl, halogen, OH, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-4} alkanoyloxy, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4} alkanoylamino, nitro, cyano, carboxy, carbamoyl, C_{1-4} alkoxycarbonyl, thiol, C_{1-4} alkylsulfanyl, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl and sulfonamido; $-CO-C_{1-4}$ alkyl; $-CO-O-C_{1-4}$ alkyl; $-CO-O-C_{2-4}$ alkenyl; $-CO-O-(CH_2)_n$ Ph optionally substituted on Ph as defined for substitution on Ph in $R^1 = -C_{1-3}$ alkylene-Ph in this claim 1 and $n=0-4$; $-C_{1-4}$ alkylene- $CONR^4R^5$ where R^4 & R^5 are independently selected from H, C_{1-4} alkyl; and $-C_{1-4}$ alkylene- $COOR^6$ where R^6 is selected from H, C_{1-4} alkyl;

R^2 is selected from H; $-C_{1-4}$ alkyl; $-C_{1-3}$ alkylene-Ph optionally substituted on Ph as defined for substitution on Ph in $R^1 = -C_{1-3}$ alkylene-Ph in this claim 1; $-COC_{1-4}$ alkyl; and $-COOC_{1-4}$ alkyl;

20

- R^3 is selected from H; OH; CN; CF_3 ; NO_2 ; $-C_{1-4}$ alkyl; $-C_{1-4}$ alkylene- R^7 where R^7 is selected from phenyl, naphthyl, and a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 5 heteroatoms selected from O, N and S and any aryl ring in R^7 is optionally substituted as defined for substitution on the Ph group in $R^1 = -C_{1-3}$ alkylene-Ph in claim 1; R^7 : C_{2-4} alkenyl; halogen: $-(CH_2)_nCOOR^8$ where $n=0-3$ and R^8 represents H.

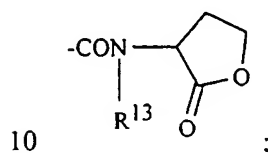
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C₁₋₄alkyl, C₂₋₄alkenyl; -CONR⁹R¹⁰ where R⁹ and R¹⁰ independently represent H, C₁₋₄alkyl, C₂₋₄alkenyl, -O-C₁₋₄alkyl, -O-C₂₋₄alkenyl, or -C₁₋₃alkylenePh optionally substituted as defined for this group for R¹ in this claim 1; -CON(R¹¹)OR¹² where R¹¹ and R¹² independently represent H, C₁₋₄alkyl and C₂₋₄alkenyl;

- 5 a group of Formula II, -CONR¹³-CHR¹⁴-COOR¹⁷, where R¹³ is H or C₁₋₄alkyl, R¹⁷ is H or C₁₋₆alkyl, R¹⁴ is selected from the side chain of a lipophilic amino acid.

carbamoylC₁₋₄alkyl, N-(monoC₁₋₄alkyl)carbamoylC₁₋₄alkyl and N-(diC₁₋₄alkyl)carbamoylC₁₋₄alkyl, the group of Formula II having L or D configuration at the chiral alpha carbon in the corresponding free amino acid; a lactone of formula



- C₁₋₄alkyl monosubstituted on carbon with =N-OH; a group of Formula -X-R¹⁵ where X is selected from O, CO, CH₂, S, SO, SO₂ and R¹⁵ is selected from C₁₋₆alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 5 heteroatoms selected from O, N and S and any aryl ring in R¹⁵ is optionally substituted as
- 15 defined for the Ph group in R¹ = -C₁₋₃alkylene-Ph in this claim 1;

p is 0-3 in which R³ values can be the same or different;

L is a linking moiety selected from the following groups written from left to right in

- 20 Formula I:

-CO-NR¹⁶- where R¹⁶ is selected from H, C₁₋₄alkyl, C₁₋₄alkylene-Z, -CO-C₁₋₄alkylene-Z, -CO-C₁₋₆alkyl, -COZ, and Z, and Z is selected from -O-C₁₋₄alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 5 heteroatoms selected from O, N and S and any aryl ring in R¹⁶ is optionally substituted as

25 defined for the Ph group in R¹ = -C₁₋₃alkylene-Ph in this claim 1; -CH₂-NR¹⁸- where R¹⁸ represents any value defined for R¹⁶; -CH₂S-; -CH₂O-; -CH₂-CHR¹⁹- where R¹⁹ represents any value defined for R¹⁶; -CH=CR²⁰- where R²⁰ represents any value defined for R¹⁶;

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- CH₂NR²¹-T- where R²¹ represents any value defined for R¹⁶. T represents -(CH₂)_n- where n is 1-4 and T is optionally monosubstituted with R²² where R²² represents any value for R¹⁶ other than H; -CH₂NR²³-SO₂- where R²³ represents any value defined for R¹⁶;
- CH₂-NR²⁴-CO-T- where R²⁴ represents any value defined for R¹⁶. T represents -(CH₂)_n- where n is 0-4 and T is optionally monosubstituted with R²⁹ where R²⁹ represents any value for R¹⁶ other than H; -CO-NR²⁵-T- where R²⁵ represents any value defined for R¹⁶. T represents -(CH₂)_n- where n is 1-4 and T is optionally monosubstituted with R²⁶ where R²⁶ represents any value for R¹⁶ other than H; -CH₂S-T- where T represents -(CH₂)_n- where n is 1-4 and T is optionally monosubstituted with R²⁷ where R²⁷ represents any value for R¹⁶ other than H; -CH₂O-T- where T represents -(CH₂)_n- where n is 1-4 and T is optionally monosubstituted with R²⁸ where R²⁸ represents any value for R¹⁶ other than H;

A is selected from phenyl; naphthyl; a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 5 heteroatoms where the heteroatoms are independently selected from O, N & S;

or a -S-S- dimer thereof when R²=H; or a N-oxide thereof;

or an enantiomer, diastereoisomer, pharmaceutically acceptable salt, prodrug or solvate thereof together with a pharmaceutically acceptable diluent or carrier.

2. A pharmaceutical composition according to claim 1 in which R¹ is selected from H; -CO-O-(CH₂)_nPh optionally substituted on Ph as defined for R¹ = -C₁₋₃alkylene-Ph in claim 1 and n=0-4; -CO-O-C₂₋₄alkenyl; -CO-C₁₋₄alkyl; -C₁₋₄alkylene-CONR⁴R⁵ where R⁴ & R⁵ are independently selected from H, C₁₋₄alkyl.

3. A pharmaceutical composition according to any one of claims 1-2 in which R² is selected from H and -CO-C₁₋₄alkyl.

4. A pharmaceutical composition according to any one of claims 1-3 in which L is selected from -CH₂-NR¹⁸-; -CH₂NR²¹-T.

5. A pharmaceutical composition according to any one of claims 1-4 in which A is selected from phenyl, naphthyl, pyridyl and thienyl.

6. A pharmaceutical composition according to any one of claims 1-5 in which combinations of R³ and p are selected from

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- i) R^3 is selected from a group of Formula II; $-C_{1-4}alkylR^7$; $-O-R^7$ and; R^7 ; and $p=1-3$ with the proviso that one value of R^3 is a group of Formula II;
- ii) $p=0$ with the proviso that A is naphthyl and L is $-CH_2NR^{21}-T$;
- iii) $p=1$ with the proviso that R^3 = a group of Formula II and A is naphthyl.
- 5 7. A pharmaceutical composition according to claim 1 in which R^1 is selected from H; $-C_{1-4}alkyl$, $-C_{1-3}alkylene-Ph$ optionally mono or di-substituted on Ph with substituents selected from $C_{1-4}alkyl$, halogen, OH, $C_{1-4}alkoxy$, $C_{1-4}alkanoyl$, $C_{1-4}alkanoyloxy$, amino, $C_{1-4}alkylamino$, $di(C_{1-4}alkyl)amino$, $C_{1-4}alkanoylamino$, thiol, $C_{1-4}alkylthio$, nitro, cyano, carboxy, carbamoyl, $C_{1-4}alkoxycarbonyl$, $C_{1-4}alkylsulfinyl$, $C_{1-4}alkylsulfonyl$, sulfonamido; $-CO-C_{1-4}alkyl$; $-CO-O-C_{1-4}alkyl$; $-CO-O-C_{2-4}alkenyl$; $-CO-O-CH_2-Ph$ optionally mono- or di-substituted on phenyl with substituents selected from $C_{1-4}alkyl$, halogen, OH, $C_{1-4}alkoxy$, $C_{1-4}alkanoyl$, $C_{1-4}alkanoyloxy$, amino, $C_{1-4}alkylamino$, $di(C_{1-4}alkyl)amino$, $C_{1-4}alkanoylamino$, thiol, $C_{1-4}alkylthio$, nitro, cyano, carboxy, carbamoyl, $C_{1-4}alkoxycarbonyl$, $C_{1-4}alkylthiono$,
- 10 $C_{1-4}alkylsulfonyl$, sulfonamido; $-C_{1-4}alkylene-CONR^4R^5$ where R^4 & R^5 are independently selected from H, $C_{1-4}alkyl$; $-C_{1-4}alkylene-COOR^6$ where R^6 is selected from H, $C_{1-4}alkyl$;
- R^2 is selected from H; $-C_{1-4}alkyl$; $-C_{1-3}alkylene-Ph$; $-COC_{1-4}alkyl$; $-COOC_{1-4}alkyl$;
- 20 R^3 is selected from H; OH; CN; CF_3 ; NO_2 ; $-C_{1-4}alkyl$, $-C_{1-4}alkylene-R^7$ where R^7 is selected from phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 3 heteroatoms selected from O,N and S; $C_{2-4}alkenyl$; halogen; $-(CH_2)_nCOOR^8$ where $n=0-3$ and R^8 represents H, $C_{1-4}alkyl$, $C_{2-4}alkenyl$; $-CONR^9R^{10}$ where R^9 and R^{10} independently represent H, $C_{1-4}alkyl$, $C_{2-4}alkenyl$, $-O-C_{1-4}alkyl$, $-O-C_{2-4}alkenyl$; $-CON(R^{11})OR^{12}$ where R^{11} and R^{12} independently represent H, $C_{1-4}alkyl$ and $C_{2-4}alkenyl$;
- 25 a group of Formula II, $-CONR^{13}-CHR^{14}-COOR^{17}$, where R^{13} is H or $C_{1-4}alkyl$, R^{17} is H or $C_{1-6}alkyl$, R^{14} is the side chain of a lipophilic amino acid with L or D configuration at the

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chiral alpha carbon in the corresponding free amino acid; C₁₋₄alkyl monosubstituted on carbon with =N-OH; -SO-C₁₋₄alkyl; -SO₂-C₁₋₄alkyl; a group of Formula -X-R¹⁵ where X is selected from CO, CH₂, S, SO, SO₂ and R¹⁵ is selected from C₁₋₆alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 3 heteroatoms selected from O, N and S;

p is 0-3 in which R³ values can be the same or different;

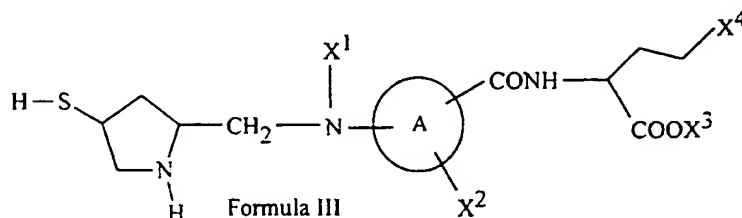
L is a linking moiety selected from the following groups written from left to right in

10 Formula I:

- CO-NR¹⁶- where R¹⁶ is selected from H, C₁₋₄alkyl, C₁₋₄alkylene-Z and Z is selected from -O-C₁₋₄alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 3 heteroatoms selected from O, N and S; -CH₂-NR¹⁸- where R¹⁸ represents any value defined for R¹⁶; -CH₂S-; -CH₂O-; -CH₂-CHR¹⁹- where R¹⁹ represents any value defined for R¹⁶; -CH=CR²⁰- where R²⁰ represents any value defined for R¹⁶; -CH₂NR²¹-T- where R²¹ represents any value defined for R¹⁶, T represents -(CH₂)_n- where n is 1-4 and T is optionally monosubstituted with R²² where R²² represents any value for R¹⁶ other than H, and provided at least one of R²¹ and R²² is H; -CH₂NR²³-SO₂- where R²³ represents any value defined for R¹⁶; -CH₂-NR²⁴-CO-T- where R²⁴ represents any value defined for R¹⁶, T represents -(CH₂)_n- where n is 0-4 and T is optionally monosubstituted with R²⁹ where R²⁹ represents any value for R¹⁶ other than H, and provided at least one of R²⁴ and R²⁹ is H; -CO-NR²⁵-T- where R²⁵ represents any value defined for R¹⁶, T represents -(CH₂)_n- where n is 1-4 and T is optionally monosubstituted with R²⁶ where R²⁶ represents any value for R¹⁶ other than H, and provided at least one of R²⁴ and R²⁵ is H; -CH₂S-T- where T represents -(CH₂)_n- where n is 1-4 and T is optionally monosubstituted with R²⁷ where R²⁷ represents any value for R¹⁶ other than H; -CH₂O-T- where T represents -(CH₂)_n- where n is 1-4 and T is optionally monosubstituted with R²⁸ where R²⁸ represents any value for R¹⁶ other than H;

A is selected from phenyl; naphthyl; a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 3 or 5 heteroatoms in the case of monocyclic and bicyclic rings respectively where the heteroatoms are independently selected from O, N & S; or a -S-S- dimer thereof when $R^2=H$.

8. A pharmaceutical composition according to any one of claims 1-7 or claim 14 which is in the form of a tablet.
9. A compound as claimed in any one of compound claims 11-13 or a compound defined in any one of pharmaceutical composition claims 1-7 for use as a medicament.
10. A compound as claimed in any one of compound claims 11-13 or a compound defined in any one of pharmaceutical composition claims 1-7 for use in preparation of a medicament for treatment of a disease mediated through farnesylation of ras.
11. A compound of any of the following classes i), ii) or iii):
class i)



15 wherein:

X^1 is selected from H; C_{1-6} alkyl; hydroxy C_{1-6} alkyl; C_{1-6} alkoxy C_{1-6} alkyl; C_{1-6} alkylcarbonyl; hydroxy C_{1-6} alkylcarbonyl; C_{1-6} alkoxy C_{1-6} alkylcarbonyl;

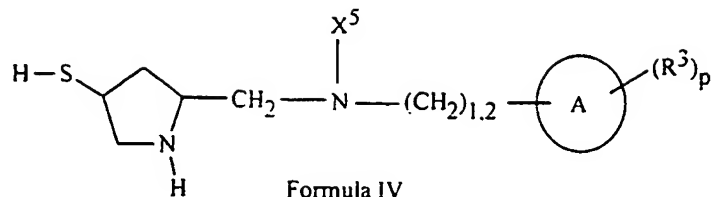
A is selected from phenyl, naphthyl or a 5-10 membered heterocyclic ring having upto 5 heteroatoms selected from O, N and S;

- 20 X^2 is selected from H; phenyl; phenyl C_{1-6} alkyl; and a 5-6 membered heteroaryl ring containing upto 3 heteroatoms selected from O, N and S optionally linked to A by C_{1-6} alkyl; and X^2 is optionally substituted on any ring, as defined for phenyl in $R^1 = -C_{1-3}$ alkylene-Ph in claim 1;

X^3 is selected from H; C_{1-6} alkyl;

- 25 X^4 is selected from C_{1-6} alkylsulfanyl; C_{1-6} alkylsulfanyl; C_{1-6} alkylsulfonyl; carbamoyl; N -(C_{1-6} alkyl)carbamoyl; N -(di C_{1-6} alkyl)carbamoyl; and hydroxy or a C_{1-4} alkyl ether thereof;
class ii)

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wherein:

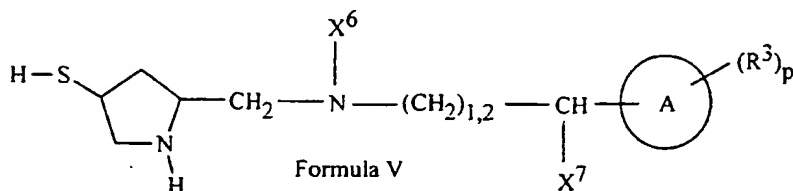
- X^5 is selected from $-\text{CO}-\text{C}_{1-4}\text{alkyl}-\text{Ph}$; $-\text{CO}-\text{C}_{1-6}\text{alkyl}$; $-\text{CO}-\text{C}_{1-4}\text{alkyl}-\text{heteroaryl}$ where heteroaryl is a 5-10 membered heteroaryl ring containing upto 5 heteroatoms selected from O, N and S and Ph or heteroaryl are optionally substituted as defined for Ph in $R^1 = -\text{C}_{1-3}\text{alkylene}-\text{Ph}$ in claim 1; $\text{C}_{1-4}\text{alkyloxyC}_{1-4}\text{alkyl}$;

A is naphthyl or a 10 membered heterocyclic ring having upto 5 heteroatoms selected from O, N and S;

R^3 and p are as defined in claim 1;

10

class iii)



wherein:

X^6 has any value defined for X^5 in ii) above;

- 15 X^7 is Ph optionally substituted as defined for Ph in $R^1 = -\text{C}_{1-3}\text{alkylene}-\text{Ph}$ in claim 1;

A is Ph or naphthyl or a 5-10 membered heterocyclic ring having upto 5 heteroatoms selected from O, N and S;

R^3 and p are as defined in claim 1;

or a N-oxide, pharmaceutically acceptable salt, prodrug or solvate thereof.

20

12. A compound according to claim 11 in which:

in compounds of class i),

X^1 is selected from H and $\text{C}_{1-6}\text{alkoxyC}_{1-6}\text{alkyl}$;

X^2 is selected from H; phenyl or phenyl $\text{C}_{1-6}\text{alkyl}$;

- 25 X^4 is $\text{C}_{1-6}\text{alkylsulfanyl}$;

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A is selected from phenyl or naphthyl;

in compounds of class ii),

p is 0 and:

in compounds of class iii)

5 X^7 is Ph;

A is Ph;

p is 0.

13. Any one of the following compounds or a pharmaceutically acceptable salt thereof:

(2S)-2-{2-Benzyl-5-[[2S,4S]-4-sulfanylpyrrolidin-2-ylmethyl)-amino]-benzoylamino}-4-

10 methylsulfanylbutyric acid methyl ester ;

(2S)-2-{2-Benzyl-5-[[2S,4S]-4-sulfanylpyrrolidin-2-ylmethyl)-amino]-benzoylamino}-4-

methylsulfanylbutyric acid ;

(2S)-2-({2-phenyl-5-[[2S,4S]-4-sulfanylpyrrolidin-2-ylmethyl)-amino]-phenylcarbonyl}-amino)-4-methylsulfanylbutyric acid methyl ester;

15 (2S)-2-({2-phenyl-5-[[2S,4S]-4-sulfanylpyrrolidin-2-ylmethyl)-amino]-phenylcarbonyl}-amino)-4-methylsulfanylbutyric acid;

(2S)-2-({3-[[2S,4S]-4-sulfanylpyrrolidin-2-ylmethyl)-amino]-naphthalene-1-carbonyl}-amino)-4-methylsulfanylbutyric acid methyl ester ;

(2S)-2-({3-[[2S,4S]-4-sulfanylpyrrolidin-2-ylmethyl)-amino]-naphthalene-1-carbonyl}-

20 amino)-4-methylsulfanylbutyric acid ;

(2S)-2-({3-phenyl-5[[2S,4S]-4-sulfanylpyrrolidin-2-ylmethyl)-amino]-phenylcarbonyl}-amino)-4-methylsulfanylbutyric acid methyl ester;

(2S)-2-({3-phenyl-5[[2S,4S]-4-sulfanylpyrrolidin-2-ylmethyl)-amino]-phenylcarbonyl}-amino)-4-methylsulfanylbutyric acid;

25 (2S,4S)-2-[{N-(4-methoxybenzyl)-N-(naphthalen-1-ylmethyl)-amino}-methyl]-pyrrolidine-4-thiol ;

N-(naphthalen-1-ylmethyl)-N-([2S,4S]-4-sulfanylpyrrolidin-2-ylmethyl)-pentanamide ;

N-(naphthalen-1-ylmethyl)-N-([2S,4S]-4-sulfanylpyrrolidin-2-ylmethyl)-2-(pyridin-3-yl)-acetamide ;

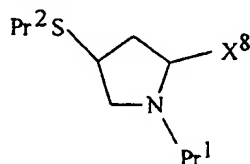
30 N-((2S,4S)-4-sulfanyl-pyrrolidin-2-ylmethyl)-3-methyl-N-(2-naphthalen-1-yl-ethyl)butyramide ;

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- \underline{N} -([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)- \underline{N} -(2-naphthalen-1-yl-ethyl)-2-pyridin-3-yl-acetamide ;
- (2S,4S)-2-{[(3-Methoxypropyl)-(2-naphthalen-1-ylethyl)amino]methyl}-pyrrolidine-4-thiol;
- 5 \underline{N} -([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-2-(4-methoxy-phenyl)- \underline{N} -(2-naphthalen-2-yl-ethyl)-acetamide ;
- (2S,4S)-2-{[(2-(4-Methoxyphenyl)ethyl)-(2-naphthalen-1-ylethyl)amino]methyl}-pyrrolidine-4-thiol ;
- \underline{N} -(2,2-Diphenyl-ethyl)- \underline{N} -([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-3-methyl-
- 10 butyramide ;
- \underline{N} -([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-3,3-dimethyl- \underline{N} -(2-naphthalen-2-yl-ethyl)-butyramide ;
- \underline{N} -(2,2-Diphenyl-ethyl)- \underline{N} -([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-3,3-dimethyl-butylamide ;
- 15 (2S)-2-{3-[[([2S,4S]-4-Sulfanyl-pyrrolidin-2-ylmethyl)-(3-methoxy-propyl)-amino]-benzoylamino]-4-methylsulfanyl-butyl}-butyric acid ;
- \underline{N} -([2S,4S]-4-Sulfanyl-pyrrolidin-2-ylmethyl)-3,3-dimethyl- \underline{N} -(2-naphthalen-1-yl-ethyl)-butyramide ;
- (2S)-4-Carbamoyl-2-({2-phenyl-5-[[([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-amino]-
- 20 phenylcarbonyl}-amino)-butyric acid; and
- (2S)-4-Carbamoyl-2-({2-phenyl-5-[[([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-amino]-phenylcarbonyl}-amino)-butyric acid methyl ester.

14. A pharmaceutical composition comprising a compound as defined in any one of
25 claims 11-13 together with a pharmaceutically acceptable diluent or carrier.

15. A process for preparing compounds of classes i). ii) or iii) as defined in claim 11 which comprises deprotecting a compound of Formula VI



Formula VI

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wherein X^8 represents the right hand side of compound classes i), ii) or iii) as defined in claim 11, Pr^1 is H or an amino protecting group, Pr^2 is H or a thio protecting group and any functional groups in X^8 are optionally protected with the proviso that there is at least one protecting group and optionally, if desired, converting the product thus obtained into a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No

PC 1/GB 96/01810

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D207/12 C07D401/12 C07D409/12 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	EP 0 696 593 A (SQUIBB BRISTOL MYERS CO) 14 February 1996 cited in the application see the whole document ---	1-15
A	WO 94 04561 A (UNIV TEXAS ;GENENTECH INC (US); BROWN MICHAEL S (US); GOLDSTEIN JO) 3 March 1994 see page 37 - page 38 ---	1-15
P,A	WO 96 09821 A (MERCK & CO INC ;ANTHONY NEVILLE J (US); DESOLMS S JANE (US); GRAHA) 4 April 1996 see page 39 --- -/--	1-15



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search

24 October 1996

Date of mailing of the international search report

31.10.96

Name and mailing address of the ISA

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Kissler, B

INTERNATIONAL SEARCH REPORT

International Application No
PC1/GB 96/01810

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 09000 A (MERCK & CO INC ;DESOLMS S JANE (US); GIULIANI ELIZABETH A (US); GR) 6 April 1995 see page 53	1-15
A	WO 95 09001 A (MERCK & CO INC ;DESOLMS S JANE (US); GARSKY VICTOR M (US); GIULIAN) 6 April 1995 see claims 10-13	1-15

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 96/01810

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
Claims searched incompletely: 1-10, 13, 15
Please see attached sheet ./.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

Obscurity

The generic formula I contains almost no fixed structural moiety. In addition, the large number of values for most of the variables, in conjunction with their cascading meanings, renders the scope of the invention for which protection is sought ill-defined and obscure. Consequently, a complete search is precluded for practical and economic reasons.

Guided by the spirit of the application and the inventive concept as disclosed in the descriptive part of the present application the search has been limited to the following case(s):

Formulae III, IV and V as defined in claim 11

(Cf. Arts. 6, 15 and Rule 33 PCT, Guidelines Exam. Part B, Chapt. III, 3.6, 3.7)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PC1/GB 96/01810

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0696593	14-02-96	AU-A- 2845395 CA-A- 2155448 JP-A- 8059610	22-02-96 12-02-96 05-03-96
WO-A-9404561	03-03-94	AU-A- 4839193 CA-A- 2142990 EP-A- 0656903 JP-T- 8500828	15-03-94 03-03-94 14-06-95 30-01-96
WO-A-9609821	04-04-96	AU-A- 3685795	19-04-96
WO-A-9509000	06-04-95	US-A- 5468733 AU-A- 7843594 EP-A- 0730467	21-11-95 18-04-95 11-09-96
WO-A-9509001	06-04-95	AU-A- 7923494 EP-A- 0725650	18-04-95 14-08-96

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